A Dissertation on

Role of DTI in Epilepsy

Submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY
CHENNAI – 600032

In partial fulfilment of the Regulations
For the Award of the Degree of

M.D. BRANCH - VIII

M.D. –Degree (RADIO-DIAGNOSIS)

DEPARTMENT OF RADIODIAGNOSIS
STANLEY MEDICAL COLLEGE
CHENNAI – 600 001

APRIL 2016

CERTIFICATE BY THE INSTITUTION

This is to certify that **Dr. PREM CHAND,** Post - Graduate Student (July 2013 to April 2016) in the Department of Radio-diagnosis STANLEY MEDICAL COLLEGE, Chennai- 600 001, has done this dissertation on "**Role of DTI in Epilepsy"** under my guidance and supervision in partial fulfillment of the regulations laid down by the Tamilnadu Dr. M. G. R. Medical University, Chennai, for M.D. (Radio-diagnosis), Degree Examination to be held in April 2016.

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DECLARATION

I, **Dr. PREM CHAND,** declare that I carried out this work on "**Role of DTI in Epilepsy** " at the department of Radiodiagnosis Government Stanley Hospital. I also declare that this bonafide work or a part of this work was not submitted by me or any other for any award, degree, or diploma to any other university, board either in India or abroad.

This is submitted to The Tamilnadu DR.M.G.R. Medical University, Chennai in partial fulfilment of the rules and regulation for the M. D. Degree examination in Radio-diagnosis.

DR. PREM CHAND

ACKNOWLEDGEMENT

At the outset I thank our Dean **Dr. ISAAC CHRISTIAN MOSES M.D.,FICP.,FACP.,** for permitting me to carry out this study in our hospital.

I express my profound thanks to my esteemed Professor and Head **Dr. C. AMARNATH, M.D., FRCR.,** Professor and HOD of Radiodiagnosis, Stanley Medical College Hospital, for encouraging and extending invaluable guidance to perform and complete this dissertation.

I immensely thank my chiefs **Dr. G. SATHYAN, M.D.,** and **Dr. B. SUHASINI. M.D., FRCR.,** Associate Professors of Radiodiagnosis for their constant encouragement and guidance throughout the study.

I wish to thank **Dr. R. GANGADEVI, M.D., F.R.C.R., Dr. K. SHIVASHANKAR, D.M.R.D., DNB., Dr. V. SUDHAKAR ,MDRD., Dr. BALAJI, M.D., Dr. S. KOMALAVALLI M.D. and Dr. K. SIVA KUMAR M.D,** Assistant Professors of Department of Radiodiagnosis, Stanley Medical College Hospital for their valuable suggestions, encouragement and advice.

I sincerely thank the members of Institutional Ethical Committee, Stanley Medical College for approving my dissertation topic.

I thank all my colleagues and para medical workers for their support.

Last but not the least, I sincerely thank all those **patients** who participated in this study, for their co-operation.

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ABSTRACT

Role of DTI in Epilepsy

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INSTITUTION: STANLEY MEDICAL COLLEGE

Background:

Diffusion Tensor Imaging (DTI) is a new non invasive MRI technique which provides insight into the white matter microstructure. In focal epilepsy widespread DTI abnormalities have been reported. In mesial temporal lobe sclerosis (MTLS) patients, although conventional MRI only shows unilateral involvement of the hippocampal sclerosis, DTI was found to be useful in demonstrating the spread of epileptiform activity to other regions of brain as well.

Aim and Objectives:

We aimed to prove this hypothesis by assessing DTI measurements in various portions of the brain in MTLS patients.

Material and methods:

We retrospectively evaluated 21 patients with unilateral MTLS by using DTI, MRI, clinical and EEG parameters. Of these 10 were Right sided and 11 were left sided MTLS. We compared the mean diffusivity (trace D) and fractional anisotropy (FA) from symmetrical voxels by sampling the following areas namely middle cerebellar peduncle, corpus callosum ,uncinate fasciculus, inferior fronto occipital fasciculus , inferior

temporo-occipital fasciculus, parahippocampal white matter, fimbria and fornix , hippocampus cingulated gyrus ,thalamus, internal capsule, caudate and lentiform nucleus . We compared these measurements with the EEG, high-resolution MR imaging, and clinical information.

Results:

There was statistically significant decrease in FA values with increased mean diffusivity was seen in the regions beyond the structurally abnormal hippocampus which could not be picked up by conventional MRI.

Conclusion: DTI is highly sensitive to cortical micro structural changes that underlie epilepsy. DTI is an important radiological tool in the pre surgical evaluation of epilepsy and surgical planning.

Introduction

A seizure is defined as the signs/symptoms caused by the abnormal excessive neuronal activity in the brain. Epilepsy is the tendency to have unprovoked seizures. About 1% of people worldwide are suffering from epilepsy and the sensitivity of conventional MRI with the current epilepsy protocol in identifying the epileptogenic focus is only slightly greater than 50%. So there is a need for additional sequences like diffusion tensor imaging in cryptogenic cases of epilepsy.

The most common form of focal epilepsy is Temporal lobe epilepsy .The etiology can be varied like hippocampal sclerosis, malformations of cortical development, mass lesions, AV malformations, gliosis etc. Previous studies with diffusion tensor imaging have shown increased apparent diffusion coefficient and decreased fractional anisotropy in the seizure focus[3].Though the origin of seizure activity is focal, there is widespread propagation of synchronized neuronal firing in seizure disorders via neuronal networks and other cortical and subcortical regions of the brain are affected[9].These widespread changes may be reflected as altered diffusion tensor imaging metrics.

Diffusion weighted imaging was introduced in 1986 by Le Bihan et al. By introducing directionality into diffusion weighted images, diffusion tensor images are obtained[1]. It assesses the molecular and biochemical environment of cerebral tissue noninvasively and is capable of demonstrating microstructural alterations in a variety of disorders.

Colour coded fractional anisotropy maps and diffusion tensor imaging tractography are used in depicting the relationship of masses to adjacent white matter tracts for presurgical evaluation[3]. Diffusion tensor imaging metrics such as fractional anisotropy and apparent diffusion coefficient have also been used to differentiate solitary metastasis from gliomas[3].

White matter abnormalities in fornix, uncinate and arcuate fasciculus, inferior longitudinal fasciculus, motor projection fibres and the cerebellum are correlated with the cognitive performance[16].Abnormalities in the uncinate fasciculus has been shown to be associated with memory, social anxiety, depression and anxiety[15]. These white matter tracts are shown to be involved in temporal lobe epilepsy and evaluation of these regions by diffusion tensor imagingmay provide useful information as to the diffuse changes in the brain that may accompany TLE.

To date, there are many diffusion tensor imaging studies in the hippocampus and extra temporal grey and white matter in patients with temporal lobe epilepsy. However, the results are variable[20]. Moreover, to the best of our knowledge, there are no published DTI studies in Indian patients with temporal lobe epilepsy on the widespread changes in grey and white matter.

We have intended to explore the utility of diffusion tensor imaging in temporal lobe epilepsy, and depict the focal and widespread abnormalities that occur in temporal lobe epilepsy in both hippocampal and extra hippocampal cases in our population. The study might establish the diagnostic value of diffusion tensor

imaging in epilepsy, and incorporate it in routine protocol. DTI might show the extent of microstructural alterations when the imaging features are normal.

HYPOTHESIS:

1. Mean diffusivity is increased and fractional anisotropy is decreased in hippocampus in patients with unilateral mesial temporal sclerosis and these change in diffusion tensor matrics are more on ipsilateral side.
2. Altered diffusion tensor imaging metrics are seen in extra temporal regions in patients with temporal lobe epilepsy and these change are more on ipsilateral side.

NEED FOR THE STUDY:

1. To explore the role of diffusion tensor imaging of hippocampus in temporal lobe epilepsy and establish the diagnostic value in regular epilepsy protocol.
2. To prove/disprove that various white matter tracts and deep grey matter show altered diffusivity in cases with temporal lobe epilepsy. This could help in determining the disease extent and in prognostication.
3. To prove / disprove that the changes in various white matter tracts and deep grey matters are more toward ipsilateral side.

AIMS & OBJECTIVES:

1. To compare the fractional anisotropy and mean diffusivity of ipsilateral and contralateral hippocampus of unilateral temporal lobe epilepsy patients with controls.
2. To analyse the fractional anisotropy (FA) and mean diffusivity (ADC) of various white matter tracts and the deep grey matter of unilateral temporal lobe epilepsy patients with contralateral side.

Materials and methods

Study area:

The study was conducted in the Department of Radiology, Stanley Medical College and Hospital, Chennai, a tertiary care hospital.

The study was approved by our scientific committee and ethical committee clearance was obtained.

Study design and period:

This study was done as an analytic, prospective case control study for a period of 3 years from June 2013 to June 2015.

Study population:

Patients with a clinical picture of temporal lobe epilepsy, referred to our department for an MRI examination and MRI examination confirms the temporal lobe epilepsy. The patients were referred from neurologists, neurosurgeons and general physicians. Irrespective of treatment status, both previously treated and untreated patients were included in the study.

Cases:

Inclusion criteria:

Adults, both males and females, with a clinical history of unilateral temporal lobe epilepsy and confirmed structural abnormalities in temporal lobe on MR imaging and EEG consistent with temporal lobe epilepsy.

Exclusion criteria:

1. Presence of intraaxial structural abnormalities in locations other than temporal lobe, as it might interfere with the diffusion tensor imaging values.
2. Presence of a major psychiatric disorder, as uncinate fasciculus is shown to be involved in psychiatric disorders.

Final case group consisted of 21 patients with unilateral temporal lobe epilepsy, 10 males and 11 females, aged between 17 to 49 years, with a mean of 33.48 yrs.

All patients underwent conventional MRI, temporal lobe protocol and diffusion tensor imaging. All of them were seizure free for more than a week at the time of imaging. The duration of seizures ranged from one month to 15 years.

Controls:

Our control group consisted of age matched adults with no neurologic deficit and normal by MR imaging.

Our control group consisted of 10 adults, of whom 4 were males and 6 were females, aged between 20 to 47 years, with a mean of 32.9 years.

There was no statistically significant difference between the ages of the two groups. The control group underwent conventional MRI and diffusion tensor imaging.

Consent: Written informed consent was obtained from cases and controls.

Imaging protocol:

The examinations were performed in 1.5T SIEMENS, MEGNETOM MRI system, using the head coil. Our conventional imaging protocol consists of T1W sequence in the sagittal plane, T2W in the axial plane and FLAIR in the coronal plane.

Parameters for conventional imaging

	T1W sagittal	T2W axial	FLAIR coronal
TR	429 ms	3000 ms	11000 ms
TE	12 ms	80 ms	100 ms
TI			2800 ms
Matrix	320 x 256 mm	420 x270 mm	244 x 152
Slice thickness	4 mm	4 mm	5mm
Slice gap	1 mm	1 mm	1 mm

Temporal lobe protocol for epilepsy consists of 3 mm oblique coronal sections orthogonal to hippocampus in T2W, T1 inversion recovery and FLAIR sequences.

Parameters for temporal lobe protocol

	T2W	T1W IR	T2WFLAIR
TR	3746 ms	1400 ms	11000 ms
TI		400 ms	2800 ms
TE	85 ms	15 ms	120 ms
Matrix	400 x 213 mm	316 x 199	336 x 210
Slice thickness	3 mm	3 mm	3 mm
Slice gap	Nil	Nil	Nil

DTI images were acquired in the axial plane using spin echo – echo planar imaging sequence using the following parameters.

TR	3500ms
TE	83 ms
FOV	224 mm
Matrix size	90 x 128 mm
Slice thickness	2.5 mm
B value	800

Diffusion sensitive gradients are applied in 21 directions.

Duration of DTI sequence is 5 minutes 19 seconds.

T1W 3D TFE imaging was done with the following parameters for superimposing over the colour coded FA maps.

TR	8.4 ms
TE	4.1 ms
Matrix	256 x 256 mm
TFE factor	131
No of slices	145

Duration of this sequence is 2 minutes 51 seconds.

Imaging is performed after a minimum of 7 days after the ictus as ADC values are known to alter in the peri ictal period.

Imaging analysis:

All DTI images were transferred to a workstation where image reconstruction and post processing analysis was performed. ROIs of similar size were placed in colour coded FA map superimposed over isotropic T1W images over bilateral hippocampi, body of fornix, para hippocampal white matter, anterior limb, genu and posterior limb of internal capsule, external capsule, genu, body and splenium of corpus callosum, thalamus, lentiform nucleus and head of caudate nucleus, frontal and occipital regions of superior longitudinal fasciculus, temporal and occipital regions of inferior longitudinal fasciculus, uncinate fasciculus, middle cerebellar peduncle and cingulum. FA and ADC values from each of these ROI was recorded.

The ROIs were placed on the axial images at the level of foramen of Munroe for anterior limb, genu and posterior limb of internal capsule, external capsule,thalamus, lentiform nucleus and head of caudate nucleus. For corpus callosum, frontal and occipital regions of superior longitudinal fasciculus, ROIs were placed on the axial images when the region was maximally seen. For

hippocampus, para hippocampal white matter, fornix and uncinate fasciculus coronal images were used. Parasagittal images were used to locate the inferior longitudinal fasciculus.

REVIEW OF LITERATURE

ANATOMY OF WHITE MATTER TRACTS:

Association fibres connect cortical areas within a hemisphere. Projection fibres connect cortical areas with deep grey matter, brainstem, cerebellum and the spinal cord. They include afferent and the efferent tracts. Commissural fibres connect corresponding cortical regions of both the hemispheres.

ASSOCIATION FIBRES:

Cingulum:

It arches over the corpus callosum. It starts beneath the rostrum of corpus callosum in the parolfactory area, courses in the cingulate gyrus, extends posteroinferiorly into the parahippocampal gyrus and the uncus connecting the frontal, parietal and the temporal lobes.

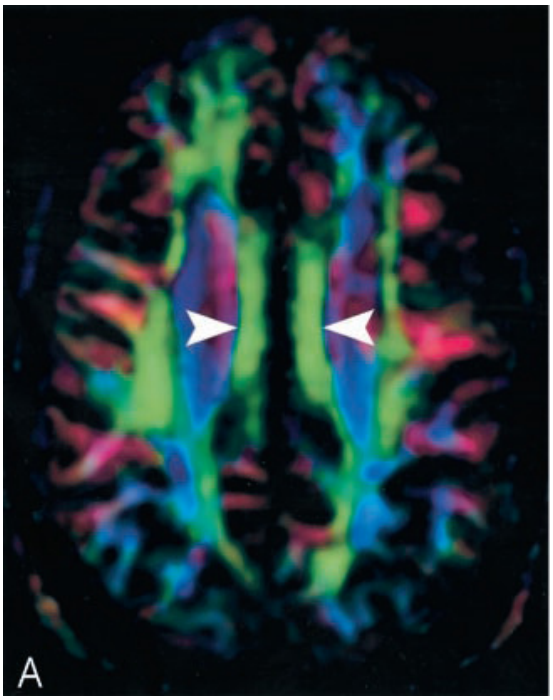


Fig 1. axial Diffusion Tensor Imaging(DTI) map showing cingulum.

Colour coded axial FA map showing cingulum (white arrowhead)

Superior longitudinal fasciculus (arcuate fasciculus): It is the largest bundle that curves along the superior margin of insula connecting the frontal lobe to parietal, temporal and the occipital lobes. A part of it is parallel to the superior occipitofrontal fasciculus and is separated from it by the corona radiata and the internal capsule.

Uncinate fasciculus:[15] It curves around the sylvian fissure connecting inferior frontal lobe with the anterior temporal lobe.

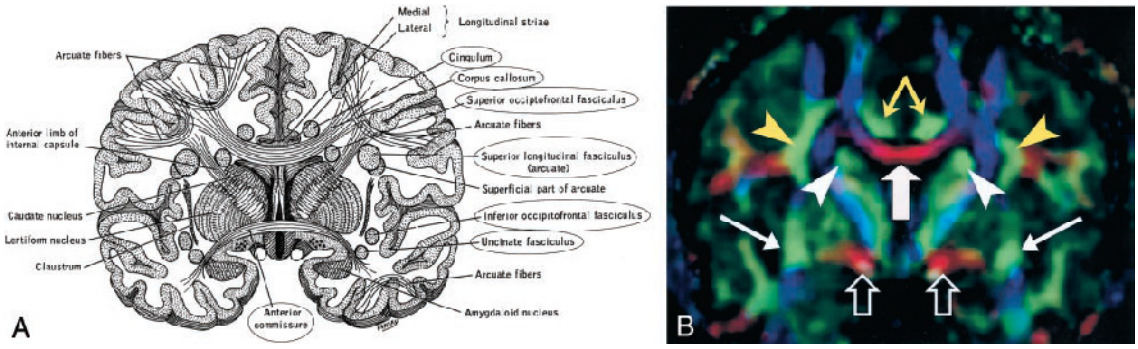


Fig 2. A & B Diagrammatic representation and colour coded coronal FA map showing uncinate fasciculus(white arrow), superior longitudinal fasciculus (yellow arrowhead), superior occipitofrontal fasciculus (white arrowhead)

Inferior longitudinal fasciculus (Occipito temporal fasciculus): It connects the occipital and the temporal lobes.

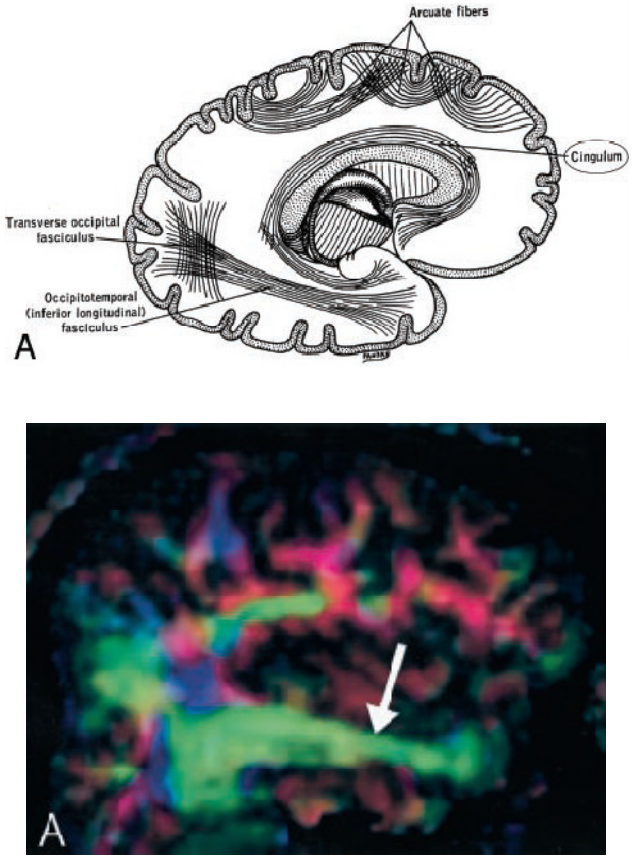


Fig 3. Diagrammatic representation and corresponding colour coded parasagittal FA map showing inferior longitudinal fasciculus (white arrow)

PROJECTION FIBRES:

Internal capsule: It is a large compact fibre bundle containing anterior limb, genu and posterior limb. The fibres of anterior limb contains fibres to and from the thalamus and the frontopontine fibres. They are anteroposteriorly oriented. Posterior limb contains corticospinal, corticobulbar and the corticopontine fibres that are superoinferiorly oriented. On colour coded FA maps, anterior limb is represented green and the posterior limb blue.

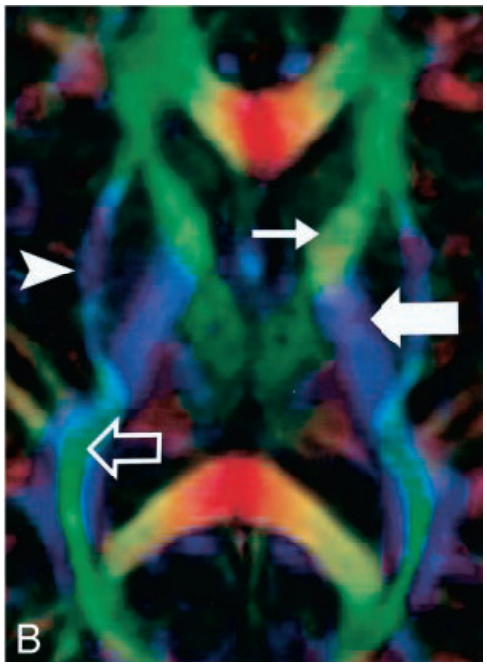


Fig 4.Colour coded axial FA map showing anterior limb (thin white arrow), posterior limb of internal capsule (thick white arrow), external capsule (white arrowhead)

COMMISSURAL FIBRES:

Corpus callosum: It is the largest white matter tract and contains a genu,body and splenium.

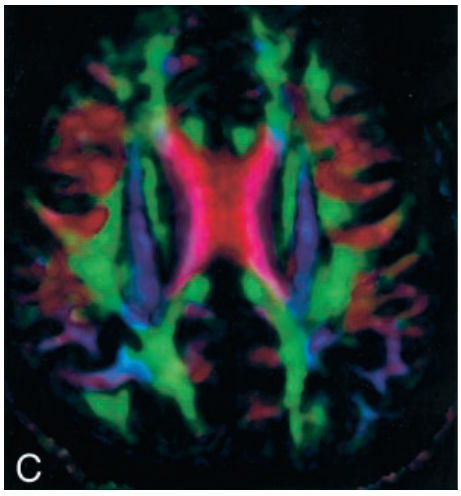


Fig 5. Colour coded axial FA map showing body of corpus callosum

Anatomy of the limbic system:[27]

Limbic lobe is phylogenetically older cortex and contains few layers than the neocortex. It plays a major role in memory, olfaction and emotion. It is composed of the hippocampus, the parahippocampal gyrus, dentate gyrus, subiculum, cingulate gyrus and the subcallosal area. Limbic system consists of the limbic lobe and some subcortical structures like the amygdala, mammillary bodies and the septal nuclei.

The limbic lobe consists of three arches surrounding the diencephalon and the basal ganglia.

The outer arch extends from the temporal to frontal lobes and consists of the uncus, parahippocampal gyrus, cingulate gyrus and the subcallosal area. The middle arch consists of the hippocampus proper (ammons horn), dentate gyrus, indusium greiseum and the paraterminal gyrus. The inner arch is the smallest and consists of fornix and fimbria, and extends from the temporal lobes to mamillary bodies.

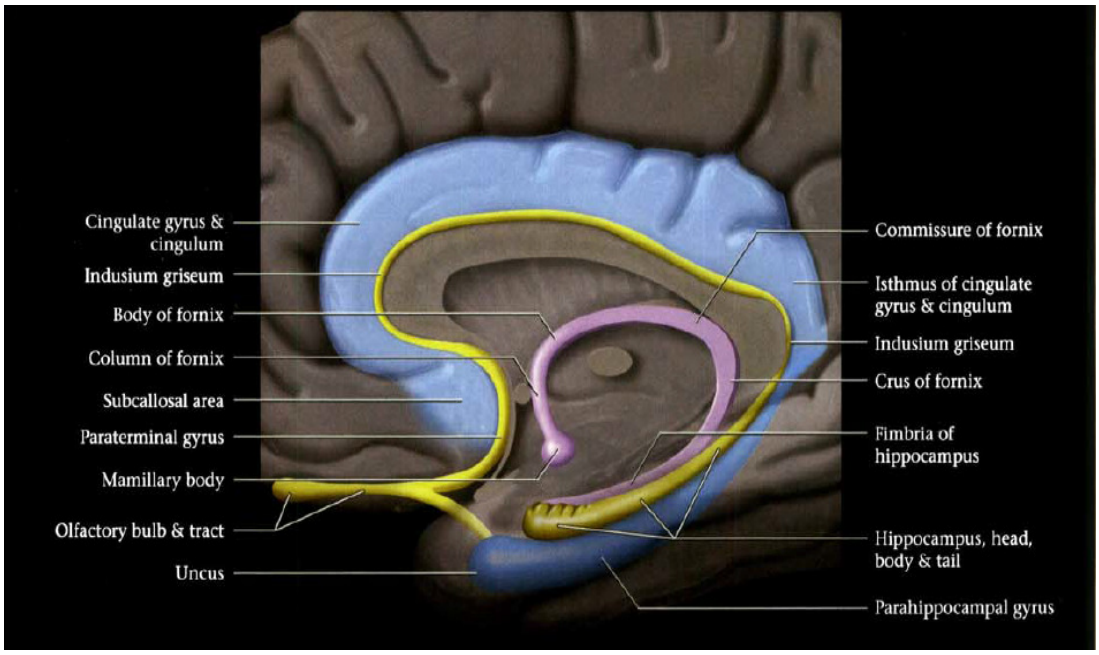


Fig 6. Diagrammatic representation of the limbic system

Imaging anatomy[27]:

Hippocampus lies on the medial aspect of temporal lobe and bulges into floor of the temporal horn. It consists of two interlocking U shaped grey matter structures, the hippocampus proper or the Ammons horn and the dentate gyrus. It has a head which consists of 3-4 digitations on the superior surface, a cylindrical body oriented parasagitally, and a tail. The Ammons horn continues laterally into the subiculum. Subiculum is the transition into the parahippocampal gyrus or the entorhinal cortex, which is part of the neocortex. A thin layer of white matter covers the hippocampus called alveus, which consists of the efferent fibres continuing as the fimbria and fornix.

Amygdala is a large grey matter nucleus which is situated anterior and superior to the hippocampus, lateral to uncus. Uncinate gyrus connects amygdala to the hippocampus.

The fimbria thickens posteriorly and splits off from the hippocampus to form the crus. The crus of the fornix attaches to the anterior surface of the splenium of corpus callosum. The crura of both sides unite to form the hippocampal commisure, and continues anteriorlyas the body.

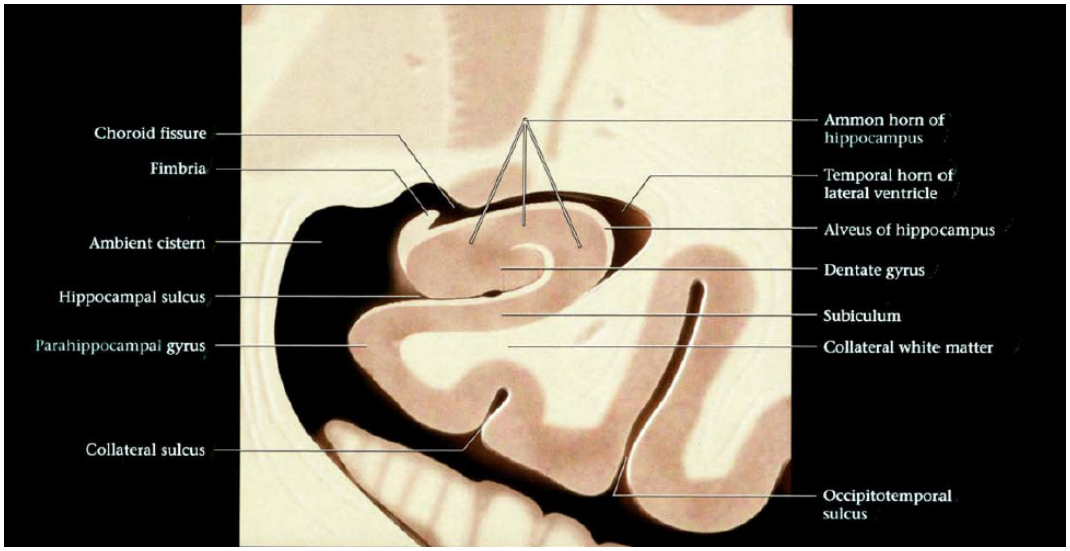


Fig 7.Coronal diagrammatic representation of the hippocampus

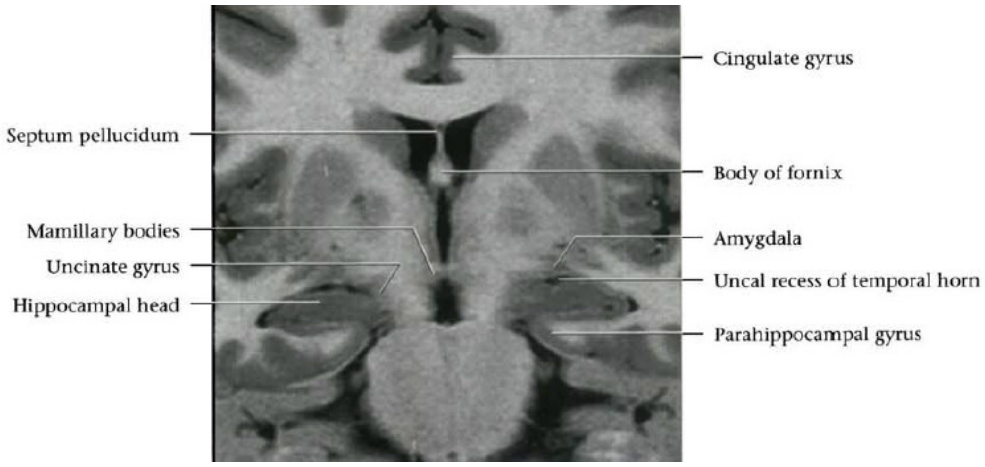
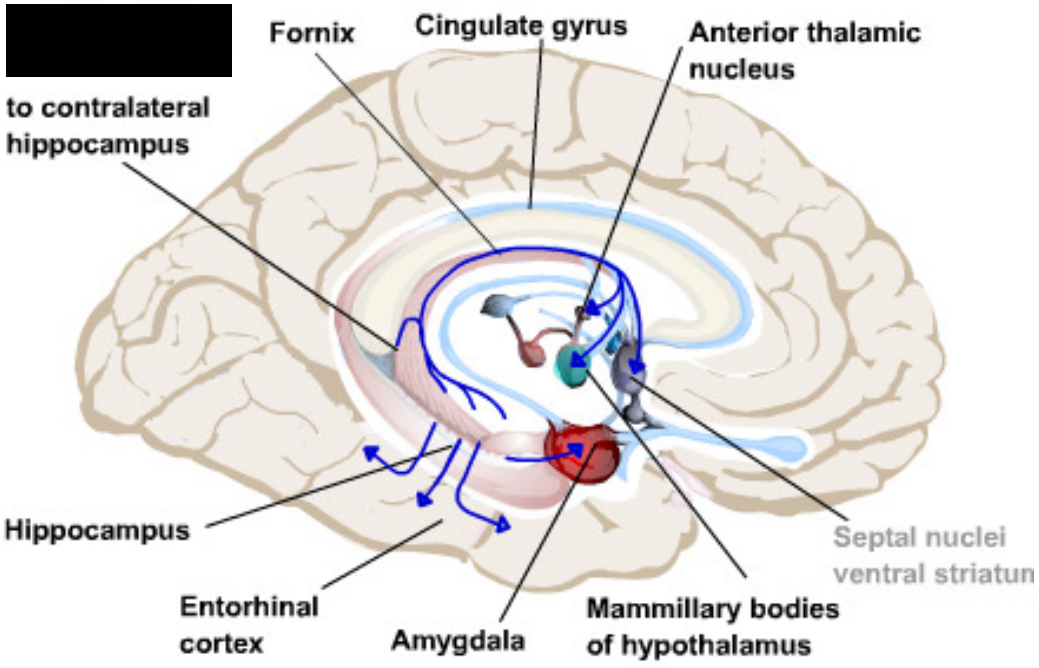


Fig 8.Coronal T1 IR image at the level of hippocampal head

Connections of the hippocampus:[26]

The hippocampus is directly connected to the parahippocampal gyrus through the subiculum, and to the amygdala through the uncinate gyrus. Two major hippocampal pathways are the fornix and the parahippocampal gyrus.

Fig 9. Output pathways of the hippocampus



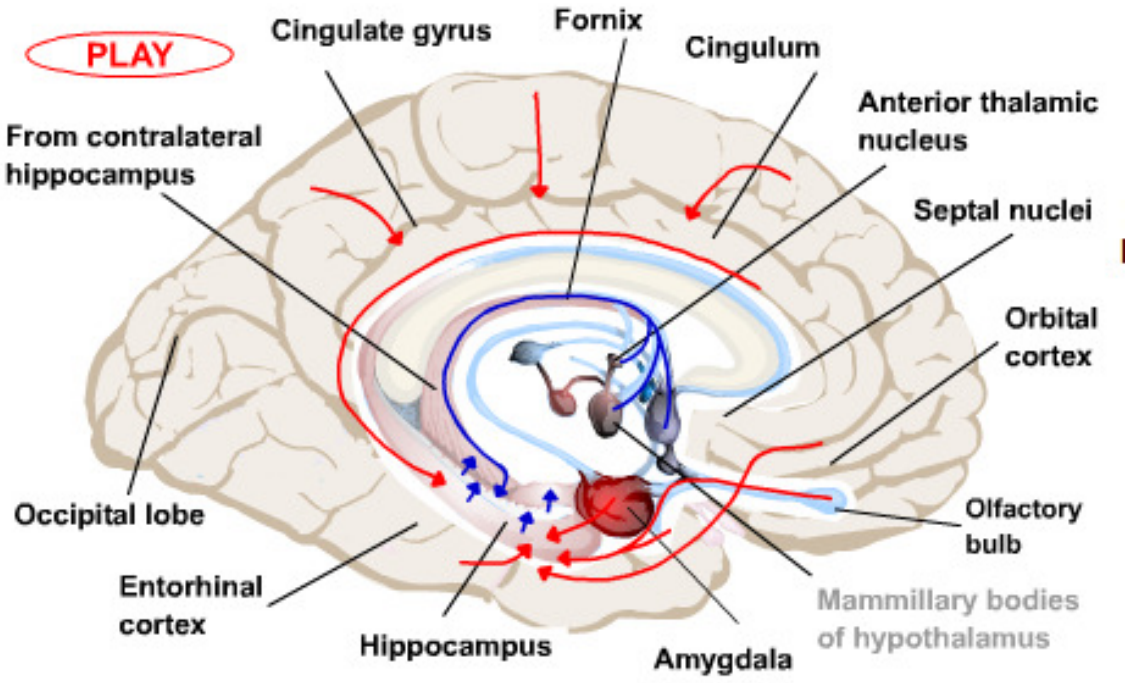
then continue as body of the fornix to the anterior commissure where it splits into three parts.

1. Precommissural fornix, just before the commissure which goes to the septal nuclei, preoptic nuclei, orbital cortex, anterior cingulate cortex and the ventralstriatum.
2. Anterior commissure, the second pathway connecting bilateral hippocampi.
3. Post commissural fornix going to mammillary bodies and the anterior nucleus of the thalamus. Anterior thalamic nuclei connect to the cingulate cortex.

The cingulate cortex in turn projects to the entorhinal cortex or the parahippocampal gyrus, completing the Papez circuit. The Papez circuit is involved in learning, memory, emotion and social behaviour.

Parahippocampal gyrus is a major source of input to the hippocampus. The cingulate gyrus, neocortex, amygdala, orbital cortex and the olfactory bulb have inputs through the parahippocampal gyrus to the hippocampus.

Fig 10.Input pathways of the hippocampus



PHYSICS:[1,8,22]

Diffusion is a process of random motion of molecules called as Brownian motion[1]. It is thermally driven, the rate of diffusion given by the equation,

$$\langle r^2 \rangle = 6Dt$$

$\langle r^2 \rangle$ denotes the mean squared displacement of the molecules, t the diffusion time and D the diffusion constant. The diffusion constant is the average displacement of the molecule in the observed time. Higher values indicate more mobility.

In the clinical setting, ADC is measured which reflects in vivo diffusion that cannot be separated from active transport, changes in membrane permeability and movement along the pressure gradient.

Stejskal – Tanner Diffusion Encoding:

A pair of diffusion sensitising, equal and opposite motion probing gradients, are applied to a T2-weighted spin-echo sequence, before and after the 180 degree refocusing pulse. If there is molecular motion, there is change in phase position during the application of diffusion sensitising gradients, resulting in incomplete rephasing and signal loss. The diffusion contrast is given by the equation,

$$S_i = S_0 \, . \, e^{-b.ADC_i}$$

S_i is the signal intensity along the direction i

S_0 is the signal intensity without the diffusion gradient

ADC_i is the ADC in the direction i

b is given by the formula,

$$b = \gamma^2 G^2 \delta^2 (\Delta - \delta/3)$$

where γ is the gyromagnetic ratio

G is the amplitude of diffusion measured in millitesla per meter

$\delta$is the duration of diffusion gradient in milliseconds

Δ is the interval between the onset of diffusion gradient before and after the rephasing pulse.

Units of b is seconds per square millimeter, ADC is millimeter square per second.

Raising b values increases the diffusion weighting.

ADC is the apparent diffusion coefficient given by the formula,

$$ADC_i = -\ln (S_i/S_0)/b$$

ln is the natural logarithm

S_i is the signal intensity in a given voxel in direction i with a given b value

S_0 is the signal intensity in a given voxel without diffusion sensitising gradients.

Isotropy and anisotropy:

The tendency of molecules to move equally in all directions is called isotropy. In brain, isotropic diffusion is seen in CSF spaces. In clinical range of b values, grey matter is considered to show isotropic diffusion. Here,the direction of diffusion sensitising gradient is considered unimportant because ADC_i is same for all directions i.

In white matter, diffusion is strongly anisotropic, occurring maximally in the same direction as white matter tracts. Larger ADC values are seen in the direction parallel to the tracts compared to the orthogonal direction. It is a property of the integrity of myelin sheath and axonal membrane[1]. So, more than one direction is required to characterise anisotropic diffusion. To overcome this problem, rotationally invariant measures like trace ADC and geometric mean DWI are used. It is derived from the DWIs in minimum of three directions S_1, S_2 and S_3

$$S_{DWI} = S_0 \cdot e^{-b.ADC}$$

Where $ADC = (ADC_1 + ADC_2 + ADC_3)/3$.

ADC is the average of three ADCs along three orthogonal directions and is rotationally invariant. It is also known as the mean diffusivity, trace ADC or ADC.

ADC mapping in healthy brain and pathology:

In clinical range of b values, in healthy adult brain, there is little difference between grey and white matter. Mean diffusivity of grey matter is 0.67-

0.83 x $10^{-3}mm^2/s$ and 0.64 – 0.71 x $10^{-3}mm^2/s$ for white matter. In neonates, ADC is very high at term, dropping steeply in first 2 years, gradually reaching the normal values in adulthood, at varying rates in different parts of the brain. ADC values tend to increase again after the age of 40.

Abnormally reduced ADC values are seen in acute cerebral ischemia, conditions causing cytotoxic edema such as status epilepticus and hypoglycemia. Infectious etiologies also cause reduced ADC measurements like abscess, subdural, intradural or intraventricular empyema. Epidermoid tumors also have restricted water motion and bright signal on diffusion weighted images. Finally, highly cellular tumors, acute demyelination, metabolic disorders, toxic exposures also have reduced diffusion.

The diffusion tensor:

White matter tracts are highly anisotropic and this property can be exploited for characterisation and anatomic mapping of these tracts. White matter is subjected to motion probing, diffusion sensitising gradients in atleast 6 non collinear directions, and with one b 0 image, a tensor is obtained. The tensor, 3 x 3 matrix of vectors is a mathematical model of 3 D diffusion anisotropy.

The diffusion ellipsoid that describes the ADC of water molecules at a particular time, is defined by 6 variables in different directions. It is a sphere for isotropic diffusion, and ellipsoid for anisotropic diffusion. The elements of a tensor above the diagonal are same as that below the diagonal, termed as conjugate symmetry.

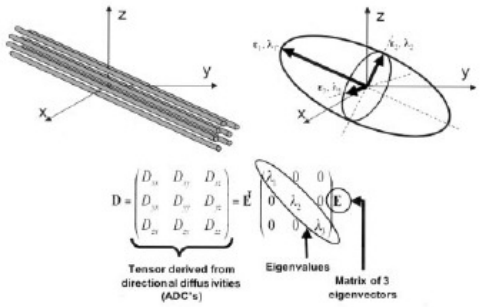


FIG 1. *Top left*, Fiber tracts have an arbitrary orientation with respect to scanner geometry (*x, y, z* axes) and impose directional dependence (anisotropy) on diffusion measurements.

Top right, The three-dimensional diffusivity is modeled as an ellipsoid whose orientation is characterized by three eigenvectors (ϵ_1, ϵ_2, ϵ_3) and whose shape is characterized three eigenvalues (λ_1, λ_2, λ_3). The eigenvectors represent the major, medium, and minor priniciple axes of the ellipsoid, and the eigenvalues represent the diffusivities in these three directions, respectively.

Bottom, This ellipsoid model is fitted to a set of at least six noncollinear diffusion measurements by solving a set of matrix equations involving the diffusivities (*ADC's*) and requiring a procedure known as matrix diagonalization. The major eigenvector (that eigenvector associated with the largest of the three eigenvalues) reflects the direction of maximum diffusivity, which, in turn, reflects the orientation of fiber tracts. Superscript *T* indicates the matrix transpose.

Diffusion tensor parameters:

By subjecting the tensor matrix to diagonalization, a set of **three Eigen values** representing major, medium and minor principle axes are obtained with their corresponding Eigen vectors. They describe the directions and lengths of the three diffusion ellipsoids axes. The largest vector is the primary Eigen vector, with its Eigen value $\lambda 1$, denotes the magnitude and direction of the greatest water diffusion. It is also termed **longitudinal diffusivity** and used in fibre tractography indicating the orientation of axons. The second and third vectors, $\lambda 2$ and $\lambda 3$ are orthogonal to the primary vectors and their mean represents **radial diffusivity.**

Trace D is the sum of the three eigen values, $D = \lambda 1 + \lambda 2 + \lambda 3$. The **mean diffusivity** is the mean of the three eigen values and is given by the formula,

$$ADC = D_{av} = \frac{\lambda 1+\lambda 2+\lambda 3}{3}$$

Fractional anisotropy (FA):

FA is derived from the standard deviation of the three Eigen values and is given by the formula,

$$FA=\sqrt{\frac{3}{2}}\, x\, \frac{\sqrt{(\lambda 1-\lambda)^2}+(\lambda 2-\lambda)^2+(\lambda 3-\lambda)^2}{\sqrt{\lambda 1^2+\lambda 2^2+\lambda 3^2}}$$

$\lambda 1, \lambda 2, \lambda 3$ *are the three eigen values and* λ *is the mean value.*

Fractional anisotropy FA ranges from 0 to 1[1].

Decreased anisotropy is a common feature of white matter tract disease. Diffusion tensor imaging exploits this property of reduced anisotropy to recognise diseased neurons before they show up on conventional imaging.

Diffusion tensor imaging in seizures:

Chen Q et al[13] in 2008 subjected 15 patients with refractory partial epilepsy and normal conventional MRI to diffusion tensor imaging in a 3T scanner. Significantly increased mean diffusivity (ADC) was observed in 13 patients of whom seven concurred with the electro clinical seizure localisation. Reduced FA was observed in five, of whom concurrence with electro clinical seizure localisation

was seen in two. They concluded that mean diffusivity is more sensitive than FA. They also observed diffusion abnormalities in the contralateral hemisphere.

During the ictal phase of seizures, there is an increase in oxygen consumption in the seizure focus, which is more than the increased blood flow. It results in relative ischemia and cytotoxic edema which is shown to result in increased ADC. As time progresses, epilepsy results in neuroglia, increased extracellular space and increased interictal ADC[9]. Anisotropic diffusion is also reduced in the white matter tracts through which the epileptiform discharges travel, reducing the FA[9].

Diffusion tensor imaging of Hippocampal formation in temporal lobe epilepsy:

The hippocampus is an important structure in temporal lobe epilepsy, and hippocampal sclerosis is the etiology in nonlesional temporal lobe epilepsy.[2]In addition to visual inspection of high resolution MR images taken orthogonal to hippocampal formation, quantification of hippocampal volume and T2 signal can increase the sensitivity of detection of hippocampal sclerosis[19]. Assaf et al [2] in 2003 analysed the mean diffusivity and fractional anisotropy of 12 patients with unilateral temporal lobe epilepsy and compared them with 14 healthy controls. They found significant increase in mean diffusivity and decreased fractional anisotropy in the Hippocampal formation of ipsilateral side compared to contralateral side in patients. Comparing with the controls, the mean diffusivity remained statistically higher but the fractional anisotropy did not reach significant differences, though they were lower.

Thivard L et al in 2005[17] with 35 patients of TLE with hippocampal sclerosis found increased diffusivity in the epileptogenic hippocampus and temporal lobe structures. The anisotropy was reduced in the ipsilateral temporal lobe. Contralateral Hippocampal formation, amygdala and rest of temporal lobe showed reduced diffusion. They found no correlation between the age at onset, duration of epilepsy and the frequency of seizures.

Diffusion tensor imaging in malformations of cortical development:

Malformations of cortical development is a common cause for epilepsy. Eriksson et al [21] in 2001, studied the diffusion tensor parameters of whole brain in patients with malformations of cortical development. They compared the diffusion tensor imaging parameters of 22 patients with seizures and malformations of cortical development using statistical parametric mapping with the parameters of 30 controls. Their patients had simple partial seizures, complex partial seizures, tonic seizures, generalised tonic clonic seizures and myoclonic jerks. They could identify reduced fractional anisotropy in 17 patients and increased mean diffusivity in 10 patients. Two patients had increased fractional anisotropy. Fractional anisotropy changes were identified beyond the conventional MRI abnormality in six patients and mean diffusivity changes were identified in nine patients.

Ictal and periictal changes in diffusion:

Seizures cause an early post ictal depression due to cytotoxic edema, followed by transient or chronic elevation of mean diffusivity.Vasogenic edema is

also noted in white matter. Duncan et al[23] reviewed various researches over a period of 2001 to 2008 and concluded that in status epilepticus, cytotoxic and vasogenic edema occur that reduce cortical diffusivity. Widespread diffusion changes were also noted in the white matter in the periictal period reflecting widespread seizure activity. In complex partial seizure, edema and hyperintensity in hippocampal formation on T2W images was correlated with reduced diffusivity.

Correlation of Diffusion tensor imaging with histopathology of fimbria- fornix in temporal lobe epilepsy patients:

Fimbria - fornixis a major afferent- efferent pathway of the hippocampus. Concha L et al [24] in 2010 studied the histopathology of fimbria - fornix in 11 medically intractable temporal lobe epilepsy patients with and without mesial temporal sclerosis. They found strong positive correlation between the fractional anisotropy of fimbria – fornix with cumulative axonal membrane circumference and axonal density. The myelin thickness was negatively correlated. The changes were bilateral suggesting etiology other than degeneration alone. Their study provides a strong validation for DTI as a measure of white matter pathology.

Extratemporal white matter in temporal lobe epilepsy:

Whatever the focus of seizure activity, there is widespread propagation of neuronal firing through white matter. This has been shown to affect the integrity of white matter in various studies.[9, 10, 11, 12, 14.] Recurrent seizures induce proconvulsant morphological changes that increase the susceptibility to network synchronisation[12].

In mesial temporal sclerosis, focal cell loss has been identified not only in hippocampal formation but also in parahippocampus, amygdala and entorhinal cortex.

Meng et al in 2010[12] studied 8 children with temporal lobe epilepsy identified by clinical criteria and EEG. MRI findings were either normal (3 patients) or had hippocampal sclerosis, cortical dysplasia, tubers and increased subcortical white matter intensity. They compared the fractional anisotropy, mean diffusivity, parallel and perpendicular Eigen values of corpus callosum, internal and external capsule of patients with the values of age and sex matched controls. The values of right and left sides had no significant differences in controls.

On ipsilateral side,they found significantly lower fractional anisotropy in anterior limb, posterior limb of internal capsule and splenium of corpus callosum. Increased mean diffusivity was noted in external capsule, anterior and posterior limb of internal capsule.A significant increase of perpendicular Eigen value was seen in external capsule, and both limbs of internal capsule. Parallel Eigen value was increased in splenium of corpus callosum. Genu of corpus callosum did not show any significant changes.

On contralateral side, there was significant alterations of diffusion tensor imaging parameters similar to the ipsilateral side. There was significant positive correlation of mean diffusivity and perpendicular Eigen value of external capsule,and perpendicular Eigen value of posterior limb of internal capsule with the age of onset of epilepsy. A significant positive correlation between parallel Eigen

value of external capsule, posterior limb of internal capsule was noted with the duration of epilepsy.

Yin X Y et al in 2014[9] studied the extra temporal abnormalities in 20 adults with unilateral temporal lobe epilepsy with 20 controls. The ROIs were anterior and posterior limbs of internal capsule, the external capsule, head of caudate nucleus, lentiform nucleus, thalamus, genu, body and splenium of corpus callosum. They measured four parameters – fractional anisotropy, mean diffusivity or ADC, parallel and perpendicular eigen values. No bilateral differences was noted in the data of either patients or controls except the thalamus which showed significant fractional anisotropy difference between the ipsilateral and contralateral sides in the patients. They found lower fractional anisotropy in all ROIs; higher ADC in bilateral external capsules, thalami,head of caudate nucleus and body of corpus callosum. They found a negative correlation between ADC of the genu of corpus callosum with the age at onset of epilepsy and a positive correlation with the duration of epilepsy.

Thalamus in temporal lobe epilepsy:

Thalamus has anatomic connection with medial temporal area and plays a role in seizure modulation[10,18]. Kim C H et al in 2010[10] studied 9 patients with hippocampal sclerosis and 9 patients with cortical dysplasia in temporal lobe neocortex. Patients were seizure free for a week before the study. All of them underwent surgery with good seizure outcome and the pathologic diagnosis was proved in all cases.

ROI was placed in centre of bilateral thalami.The mean diffusivity was increased in bilateral thalami in all patients compared to controls while the FA did not differ. Ipsilateral MD was higher in mesial temporal sclerosis cases compared to patients without hippocampal sclerosis. Age at onset, seizure duration, frequency, and total seizure number had no correlation with FA and MD.

A study by Wang et al in 2012[18] with 19 patients of TLE (8 had simple partial seizure) and 21 controls of FA and MD in bilateral thalami, normal appearing white matter in the frontal and occipital lobe, the corpus callosum, the internal capsule, the external capsule, normal appearing grey matter in the putamen, caudate nucleus demonstrated reduced FA in bilateral thalami and normal appearing white matter of posterior limb of internal capsule in patients with TLE. The thalamic involvement showed a tendency to correlate with the age at seizure onset and the duration of epilepsy.

Thivard L et al in 2005[17] with 35 patients of TLE observed the widespread diffusion tensor imaging abnormalities. Using statistic parametric mapping, they explored the whole brain parameters. Major diffusion changes in the form of reduced fractional anisotropy were identified in ipsilateral arcuate fasciculus, corpus callosum and the cingulum. No diffusion abnormalities were found in bilateral fornix and the thalamus. Ipsilateral lower mean diffusivity in sclerosed hippocampus correlated with the presence of epigastric aura.

Corpus callosum in temporal lobe epilepsy:

Corpus callosum is the largest commisural fibre and plays an important role in the transmission of epileptogenic activity to the contralateral hippocampus and lobe[11]. Tractography revealed the fibres through splenium connecting the temporal lobes.

Kim et al in 2008[11] studied 10 patients of temporal lobe epilepsy of whom two had mesial temporal sclerosis and eight had neocortical epilepsy. They compared the fractional anisotropy, apparent diffusion coefficient, parallel ($\lambda 1$)and perpendicular ($\lambda 2$ and $\lambda 3$) eigen values with those of 10 controls. They demonstrated significantly reduced fractional anisotropy in the splenium of corpus callosum. The $\lambda 1$ was decreased and $\lambda 2$ and $\lambda 3$ were increased in the splenium. They concluded the possible role of spreading seizure activity through splenium in secondary degeneration of white matter.

Cognition in temporal lobe epilepsy:

In the study by Wang et al[18], patients with temporal lobe epilepsy had poorer performance in category fluency and other executive functions. The FA of white matter of left frontal lobe and right occipital lobe correlated positively with category fluency scores. The mean diffusivity of deep grey matter structures are negatively correlated with category fluency.

Riley et al in 2010[16] studied the integrity of white matter tracts and its impact on the cognitive function in 12 TLE patients. They found white matter abnormalities in fornix, uncinate and arcuate fasciculus, inferior longitudinal

fasciculus, motor projection fibres and the cerebellum. These abnormalitiescorrelated with the cognitive performance. Alteration in the splenium of corpus callosum correlated with the age of onset.

Uncinate fasciculus connects temporal lobe with inferior frontal gyrus. Abnormalities in the uncinate fasciculus have been shown to be associated with social anxiety and depression[15]. Preferential pathway for seizure spread is the fornix, stria terminalis, amygdala fugal fibres and the uncinate fasciculus[14]. A study in 2008 by Diehl et el[14] with 28 patients of TLE showed increased ADC and reduced fractional anisotropy in these regions affected immediate and delayed auditory and visual memory.

Reference	**Age and number**	**Seizure type**	**DTI abnormalities**
Assaf et al [2], 2003	12 adults	Unilateral TLE	Increased ADC in ipsilateral hippocampus.
Thivard et al[17], 2005	35 adults	Unilateral TLE	Increased ADC in ipsilateral hippocampus, temporal lobe, reduced ADC in contralateral temporal lobe, reduced FA in ipsilateral extratemporal regions.
Kim et al[11], 2008	10 adults	Unilateral mesial, neocortical TLE	Reduced FA in splenium of corpus callosum

Diehl et al[14], 2008	28 adults	Unilateral TLE	Reduced FA and increased ADC in bilateral uncinate fasciculi, correlated with visual and auditory memory in left TLE
Knake et al[28], 2009	12 adults	Left TLE	Reduced FA in bilateral temporal lobe white matter, ipsilateral frontal lobe white matter, genu and body of corpus callosum, ipsilateral hippocampus, ipsilateral parahippocampal gyrus.
Kim et al[10], 2010	9 TLE patients with hippocampal sclerosis, 9 TLE patients without hippocampal sclerosis	Unilateral TLE	Increased ADC in bilateral thalami
Meng et al[12], 2010	8 children and adolescents	Unilateral TLE	Reduced FA in bilateral anterior and posterior limbs, genu of internal capsule, splenium of corpus callosum, increased ADC in bilateral external capsule, anterior

			and posterior limbs of internal capsule, splenium of corpus callosum.
Wang et al[18], 2012	27 adults	Unilateral TLE	Reduced FA in bilateral thalami, posterior limb of internal capsule, positive correlation between category fluency scores and FA of left frontal lobe and right occipital lobe.
Riley et al[16], 2010	12 adults	Unilateral TLE	Reduced FA in ipsilateral anterior temporal lobe, posterior mesial temporal lobe, cerebellum, contralateral fronto parietal lobe.
Yin et al[9], 2014	20 adults	Unilateral TLE	Reduced FA in internal capsule, external capsule, head of caudate nucleus, lentiform nucleus, thalamus, genu, body and splenium of corpus callosum. Increased ADC in bilateral external capsule, head of caudate nucleus, thalamus, body of corpus callosum.

STATISTICAL ANALYSIS

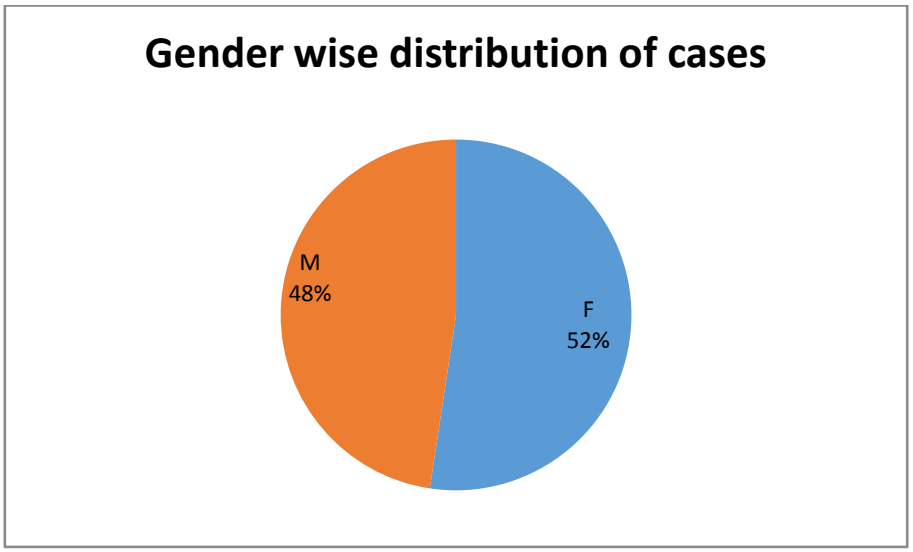
- All the continuous variables were tested for the normality using Shapiro Wilk's test.Variables were normally distributed and expressed as mean ± SD. Categorical variables were expressed either as percentage or proportion.
- Comparison of categorical variables (age) was done by Chi -square test or Fisher's exact test based on the number of observations.
- Comparison of normally distributed continuous variables between cases and controls was done by independent sample T test.
- Comparison of right and left sided variables within controls was done by paired T test.
- All the P values less than 0.05 were considered statistically significant.
- Data entry was done in MS excel worksheet.
- Data analysis was done by SPSS software version 16.0.

There are total 21 cases (10 males and 11 females) and 10 controls (3 male and 7 females)

Gender wise distribution of the study subject

		Corpus callosum (CC)		
		Cases	Controls	Total
SEX	F	11	7	18
	M	10	3	13
Total		21	10	31

F= Female , M=Male



Descriptive statics

The diffusion tensor metrics derived from all region of interest and statistical results of between different variables are listed in following tables-

Table 1. FA OF HIPPOCAMPUS AND FORNIX

Site	Cases(21)	Cases(10)	Controls(21)	Controls(10)	P value
	Mean	SD	Mean	SD	
FA of ipsilateral hippocampus	.22	.06	.18	.05	.005*
FA of contralateral hippocampus	.26	.05	.18	.05	.001*
FA of ipsilateral fornix	.37	.21	.32	.16	.000*
FA of contralateral fornix	.38	.19	.32	.16	.022

*statistically significant

Compared to controls, patients bilateral hippocampi and fimbrae and fornix had significantly reduced FA values, the values are more altered in ipsilateral side.

Figure 11. Error bar comparing FA of bilateral hippocampi of cases and controls

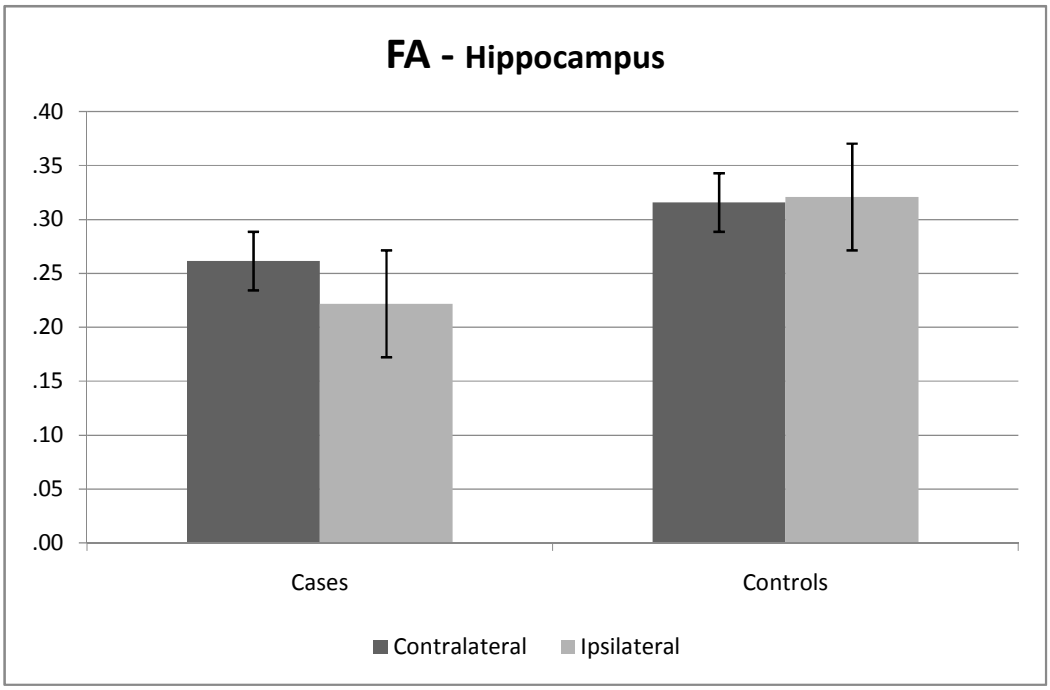


Figure 12. Error bar comparing FA of bilateral fimbrae and fornix of cases and controls

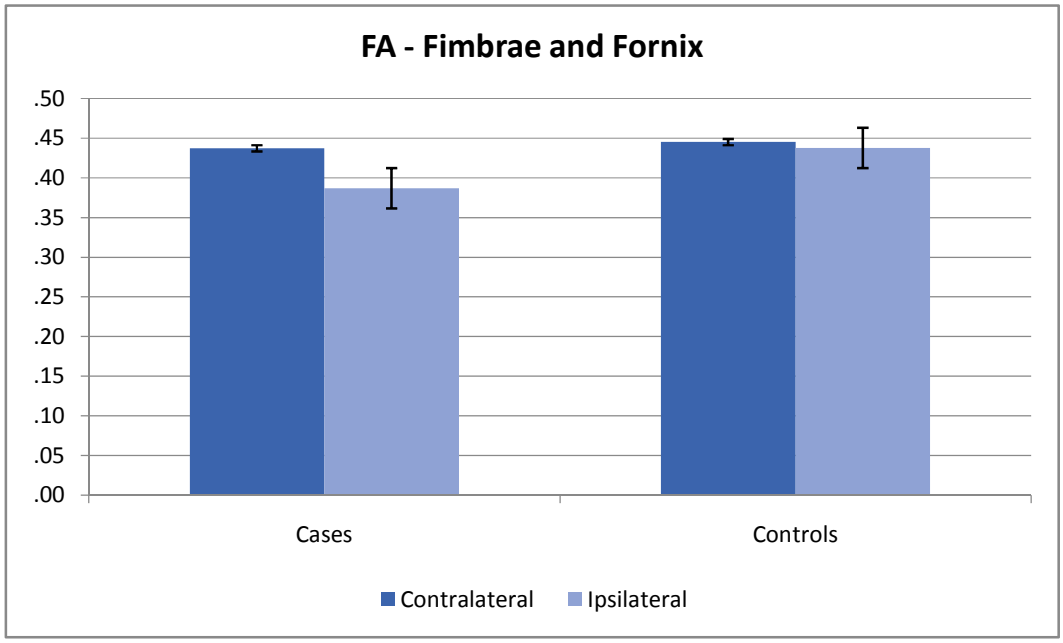


Table 2. ADC OF HIPPOCAMPUS AND FIMBRAE AND FORNIX

Site	Cases(21)	Cases(10)	Controls(21)	Controls(10)	P value
	Mean	SD	Mean	SD	
ADC of ipsilateral hippocampus	0.92	.086	.77	.025	.000*
ADC of contralateral hippocampus	.83	.03	.76	.027	.000*
ADC of ipsilateral fornix	0.87	.016	0.76	.0.38	.000*
ADC of contralateral fornix	0.76	.014	0.76	.0.42	.104

*statistically significant

Compared to controls, patients' bilateral hippocampi , fimbrae and fornix had significantly increased ADC values. But ADC of contralateral fornix doesn't achieve statistically significance. There is significant increase in ADC values on ipsilateral side compared to contralateral side.

Figure 13. Error bar comparing ADC of bilateral hippocampi of cases and controls

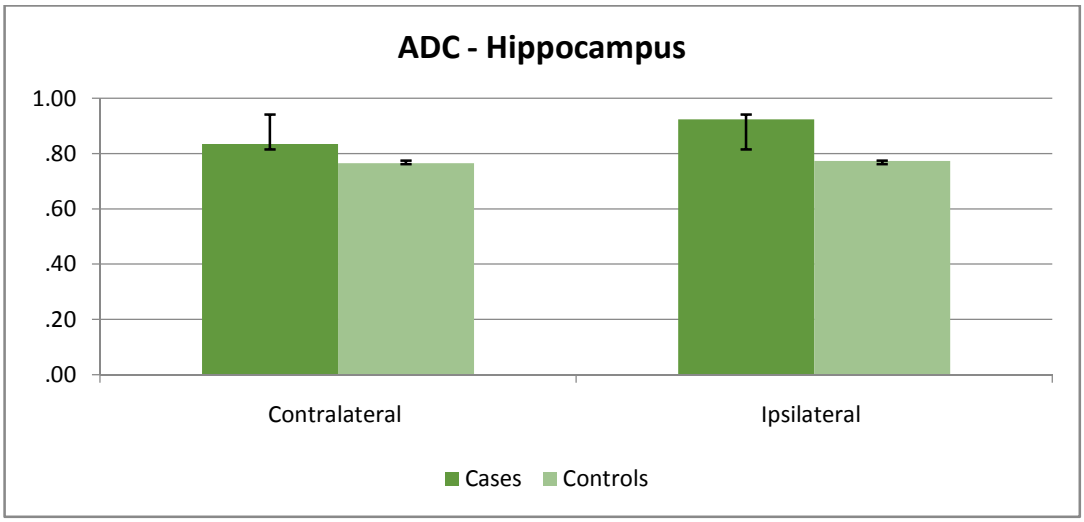


Figure 14. Error bar comparing ADC of bilateral fimbrae and fornix of cases and controls

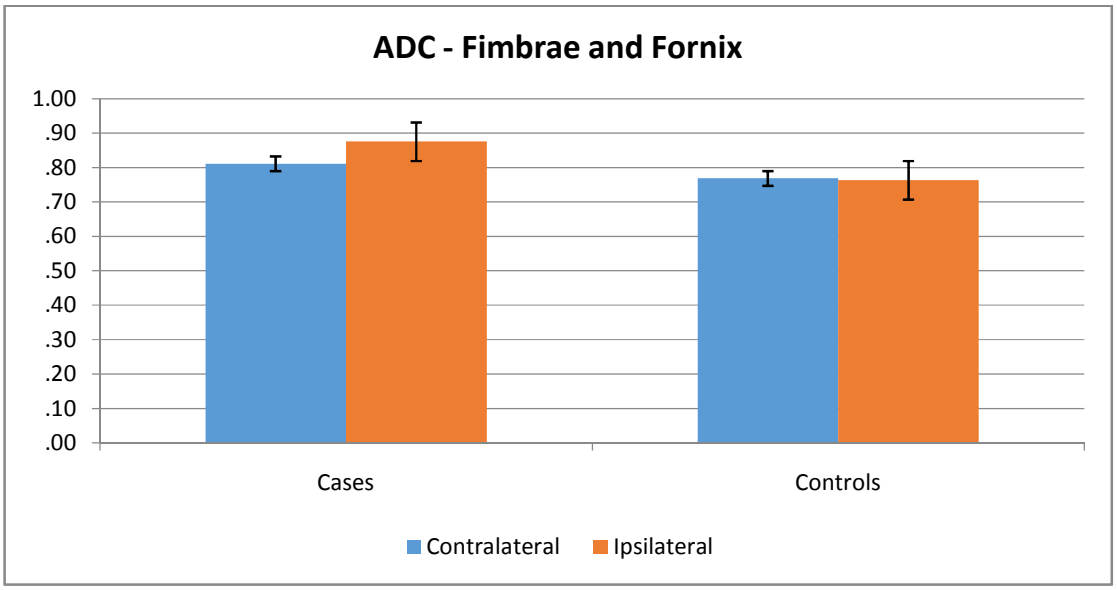


Table 3. Fractional Anisotropy (FA) VALUES OF INTERNAL CAPSULE

Site	Cases(21)	Cases(21)	Controls(10)	Controls(10)	P value
	Mean	SD	Mean	SD	
FA of ipsilateral anterior limb of internal capsule	.46	.12	.54	.12	.002*
FA of contralateral anterior limb of internal capsule	.51	.17	.54	.12	.02*
FA of ipsilateral posterior limb of internal capsule	.57	.11	.60	.07	.01*
FA of contralateral posterior limb of internal capsule	.57	.09	.57	.07	.6
*statistically significant					

Compared to controls, patient's bilateral anterior limb of internal capsule had statistically significant reduced FA values. Fractional Anisotropy (FA) of contralateral posterior limb of internal capsule was not reduced and doesn't achieve statistical significance.

Figure 15. Error bar comparing FA of bilateral anterior limbs of internal capsule of cases and controls

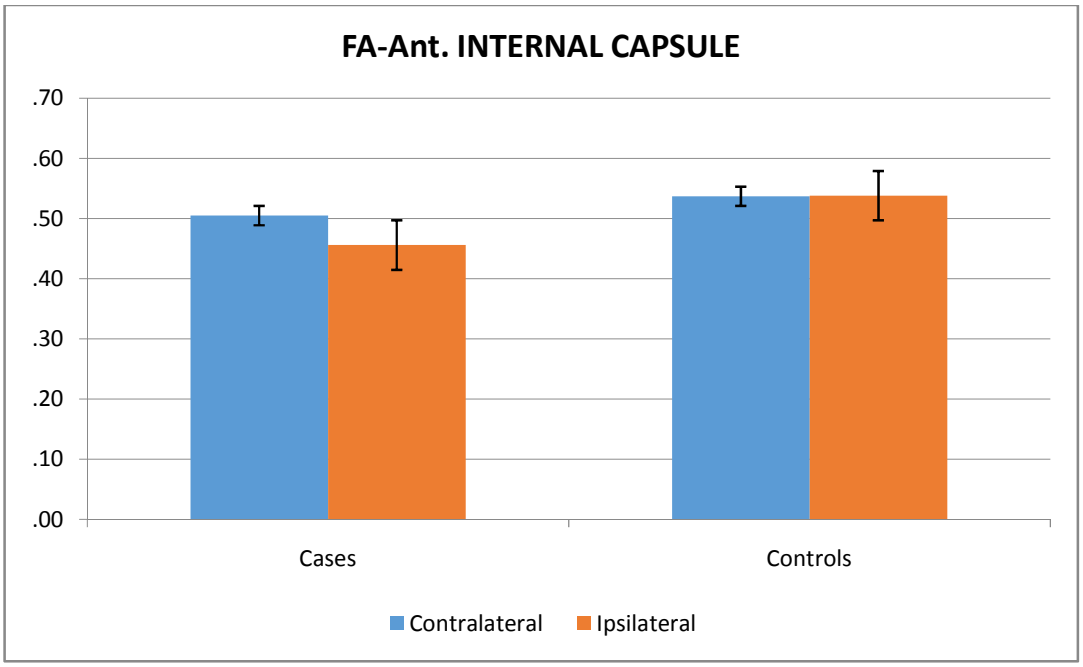


Figure 16. Error bar comparing FA of bilateral posterior limbs of internal capsule of cases and controls

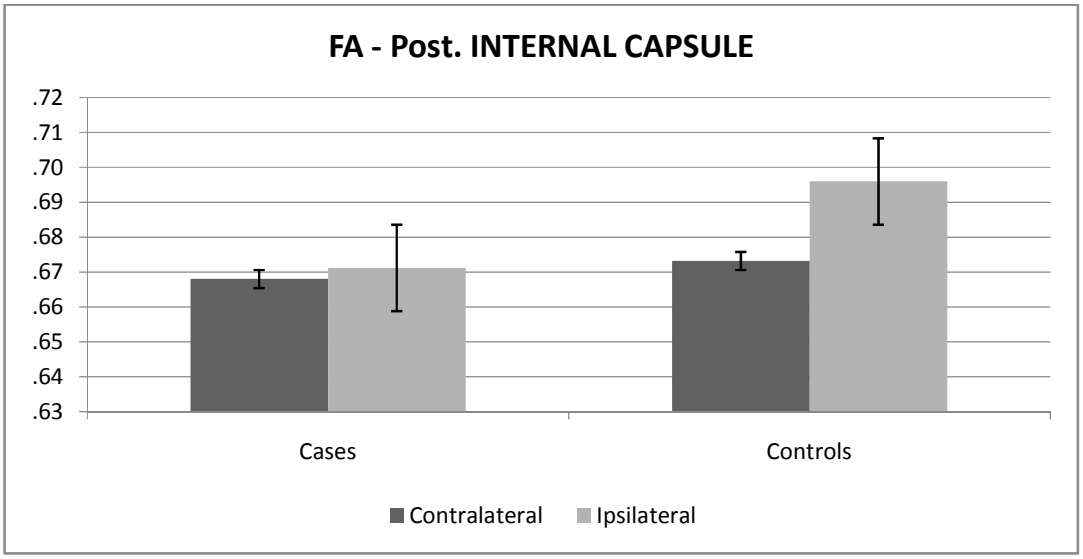


Table 4. ADC OF INTERNAL CAPSULE

Site	Cases(21)	Cases(21)	Controls(10)	Controls(10)	P value
	Mean	SD	Mean	SD	
ADC of ipsilateral anterior limb of internal capsule	.75	.22	.67	.13	.000*
ADC of contralateral anterior limb of internal capsule	.74	.16	.72	.13	.002*
ADC of ipsilateral posterior limb of internal capsule	.72	.14	.71	.10	.005*
ADC of contralateral posterior limb of internal capsule	.72	.09	.68	.10	.02*

*statistically significant

Compared to controls, patients' ADC of bilateral anterior and posterior limb of internal capsules had statistically significant lower values.

Figure.17. Error bar comparing ADC of bilateral anterior limbs of internal capsule of cases and controls

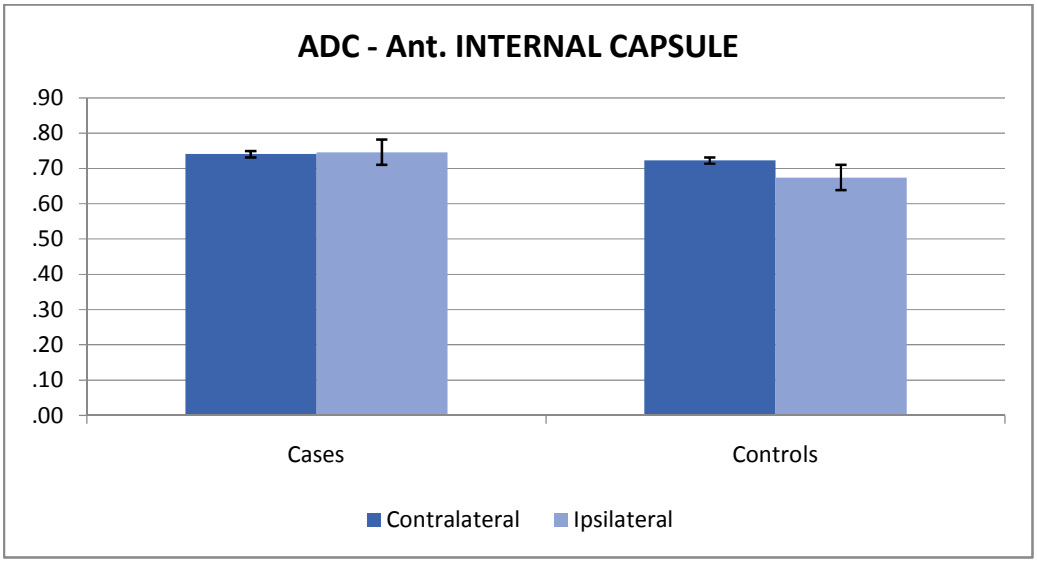


Figure.18. Error bar comparing ADC of bilateral posterior limbs of internal capsule of cases and controls

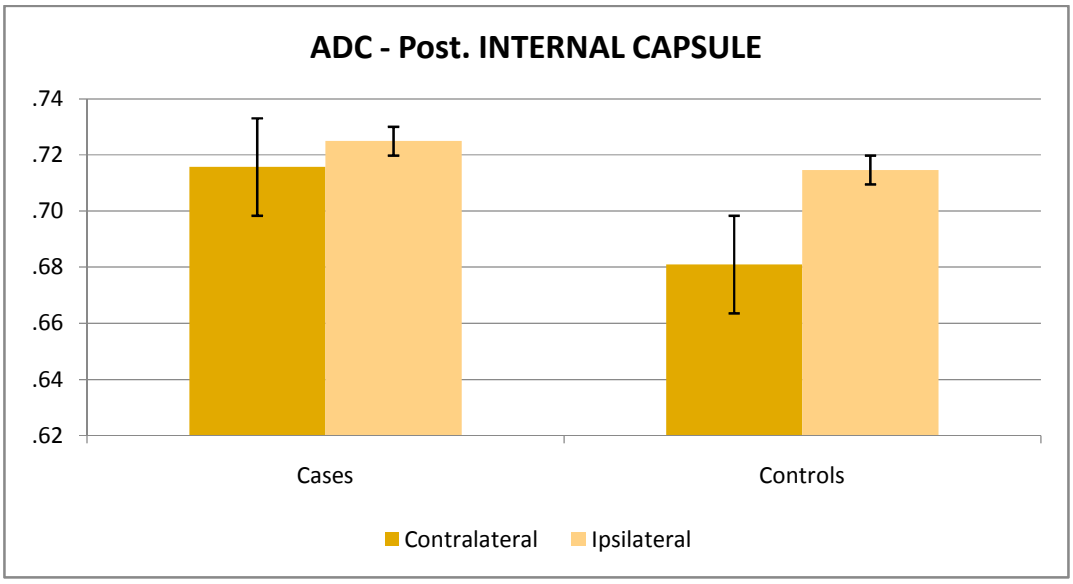


Table 5. FA& ADC OF CORPUS CALLOSUM

Site	Cases(21)	Cases(21)	Controls(10)	Controls(10)	P value
	Mean	SD	Mean	SD	
FA of genu of corpus callosum	.70	.14	.16	.02	.000*
ADC of genu of corpus callosum	.71	.18	.69	.15	.000*
FA of body of corpus callosum	.50	.74	.16	.04	.000*
ADC of body of corpus callosum	.83	.11	.71	.13	.000*
FA of splenium of corpus callosum	.76	.11	.23	.09	.000*
ADC of splenium of corpus callosum	.74	.17	.72	.16	.000*

*statistically significant

Compared to controls, patients corpus callosum had statistically significant values of increased ADC and decreased Fractional Anisotropy (FA) in body genu and the splenium.

Figure 18. Error bar comparing ADC of genu &body of corpus callosum of cases and controls

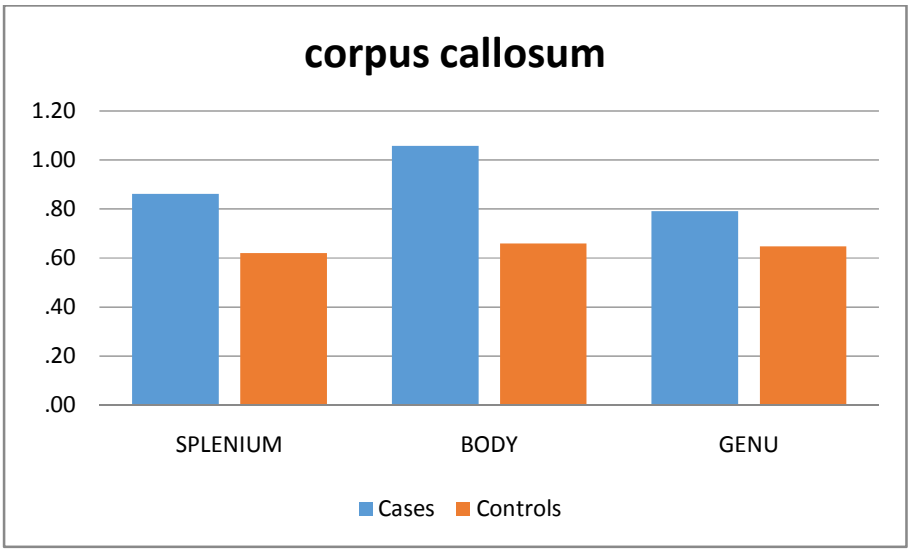


Figure 19. Error bar comparing FA of genu &body of corpus callosum of cases and controls

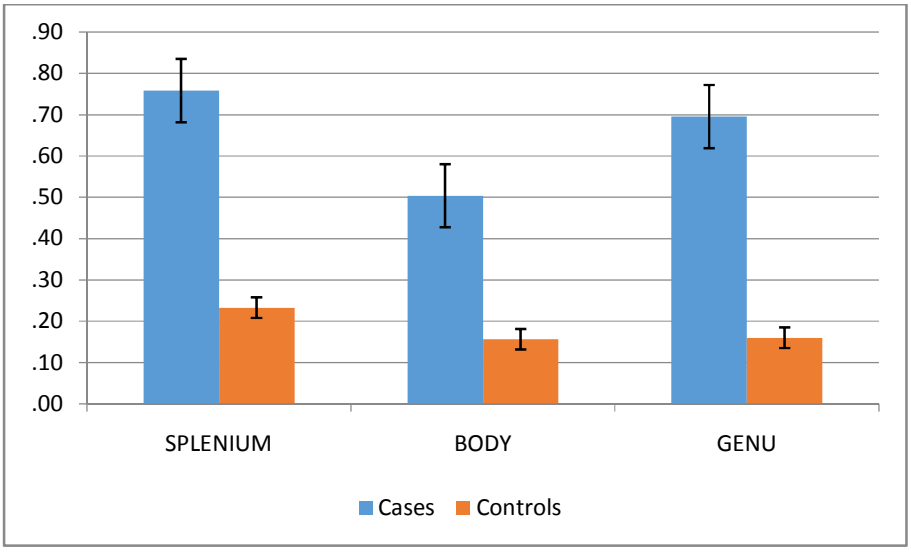


Table 6. FA OF HEAD OF CAUDATE AND LENTIFORM NUCLEUS

Site	Cases(31)	Cases(31)	Controls(30)	Controls(30)	P value
	Mean	SD	Mean	SD	
FA of ipsilateral lentiform nucleus	.12	.04	.26	.08	.000*
FA of contralateral lentiform nucleus	.13	.09	.22	.06	.000*
FA of ipsilateral head of caudate nucleus	.19	.08	.24	.10	.000*
FA of contralateral head of caudate nucleus	.19	.06	.71	.09	.000*

*statistically significant

FA of bilateral lentiform nuclei and head of caudate nucleus shows a significant changes

Figure 19. Error bar comparing FA of caudate nucleus of cases and controls

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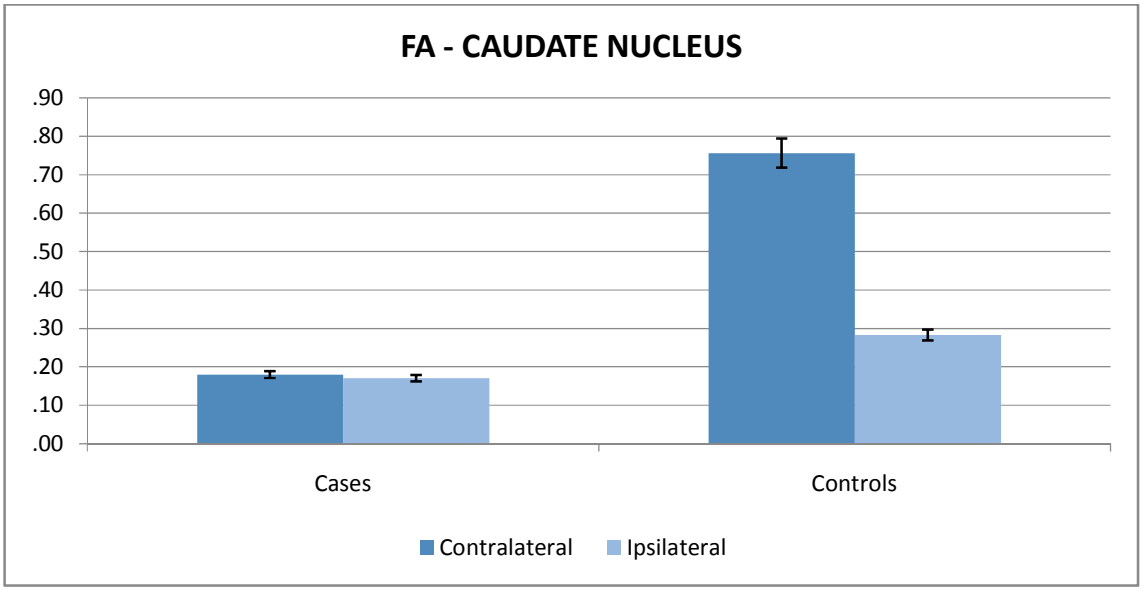


Figure 20. Error bar comparing FA of lentiform nucleus of cases and controls

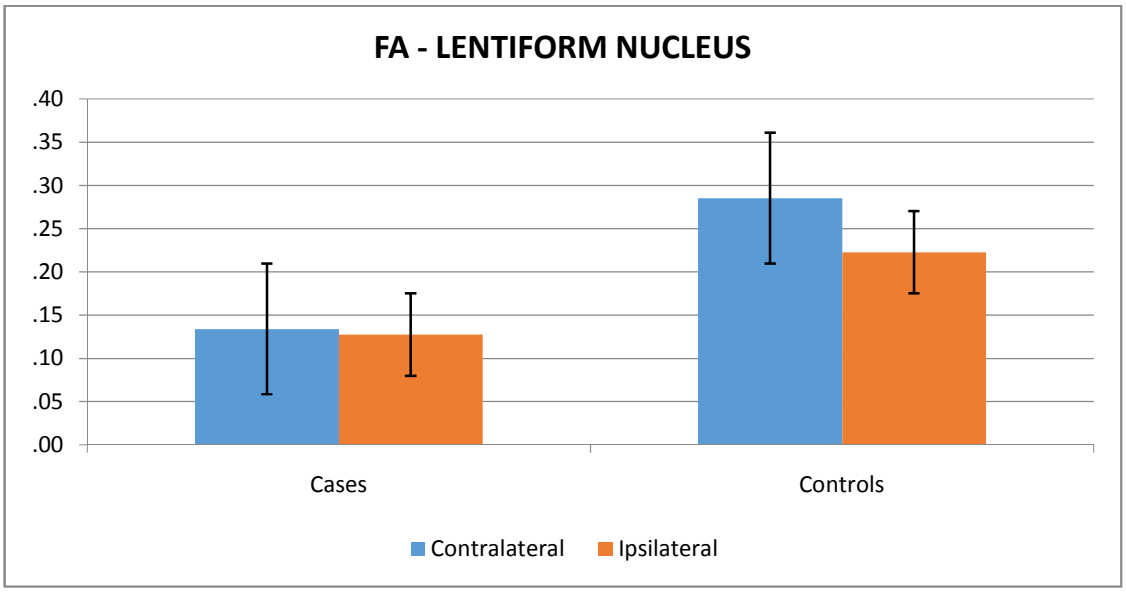


Table 7. ADC OF HEAD OF CAUDATE AND LENTIFORM NUCLEUS

Site	Cases(21)	Cases(21)	Controls(10)	Controls(10)	P value
	Mean	SD	Mean	SD	
ADC of ipsilateral lentiform nucleus	.70	.07	.61	.12	.003*
ADC of contralateral lentiform nucleus	.70	.10	.61	.12	.003*
ADC of ipsilateral head of caudate nucleus	.66	.21	.61	.13	.004*
ADC of contralateral head of caudate nucleus	.64	.17	.67	.11	.158

*statistically significant

ADC of bilateral lentiform nuclei and head of ipsilateral caudate nucleus was higher with statistical significance. ADC of contralateral head of caudate nucleus was higher but ipsilateral shows statistically significance.

Figure 22. Error bar comparing ADC of bilateral lentiform nuclei of cases and controls

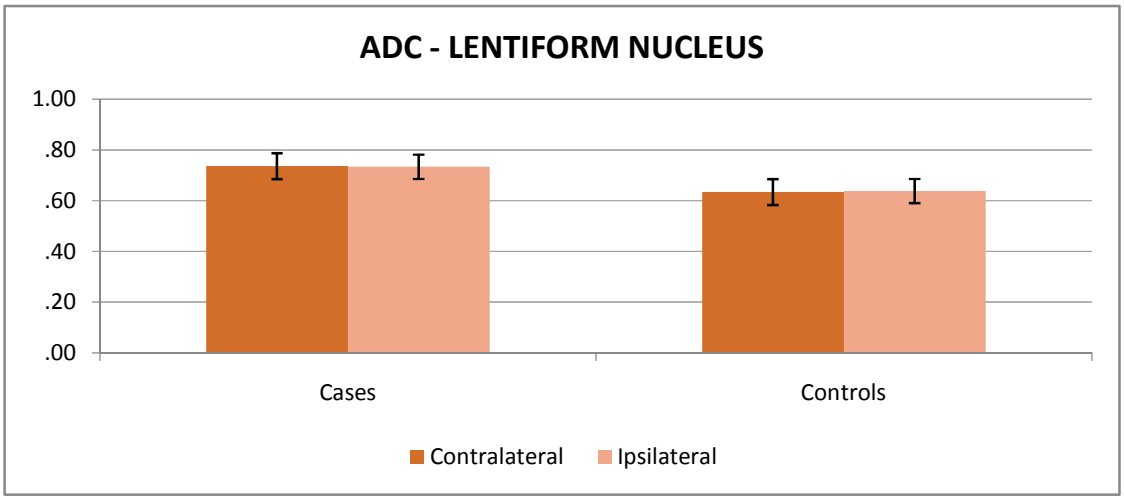


Figure 22. Error bar comparing ADC of bilateral caudate nuclei of cases and controls

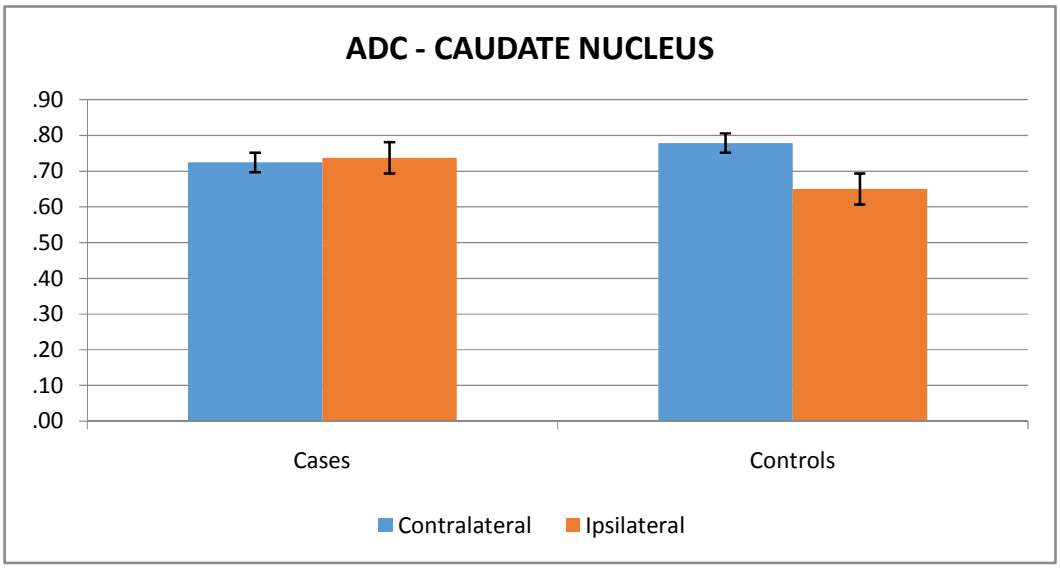


Table 8. FA & ADC OF THALAMUS

Site	Cases(21)	Cases(21)	Controls(10)	Controls(10)	P value
	Mean	SD	Mean	SD	
FA of ipsilateral thalamus	.22	.09	.44	.07	.000*
FA of contralateral thalamus	.24	.09	.82	.07	.000*
ADC of ipsilateral thalamus	.74	.16	1.02	.06	.000*
ADC of contralateral thalamus	.70	.08	.69	.06	.009*

Our study did show significant alteration in the DTI values between cases and controls in thalamus with changes are more pronounced on ipsilateral side.

Figure 23. Error bar comparing ADC of bilateral thalamus of cases and controls

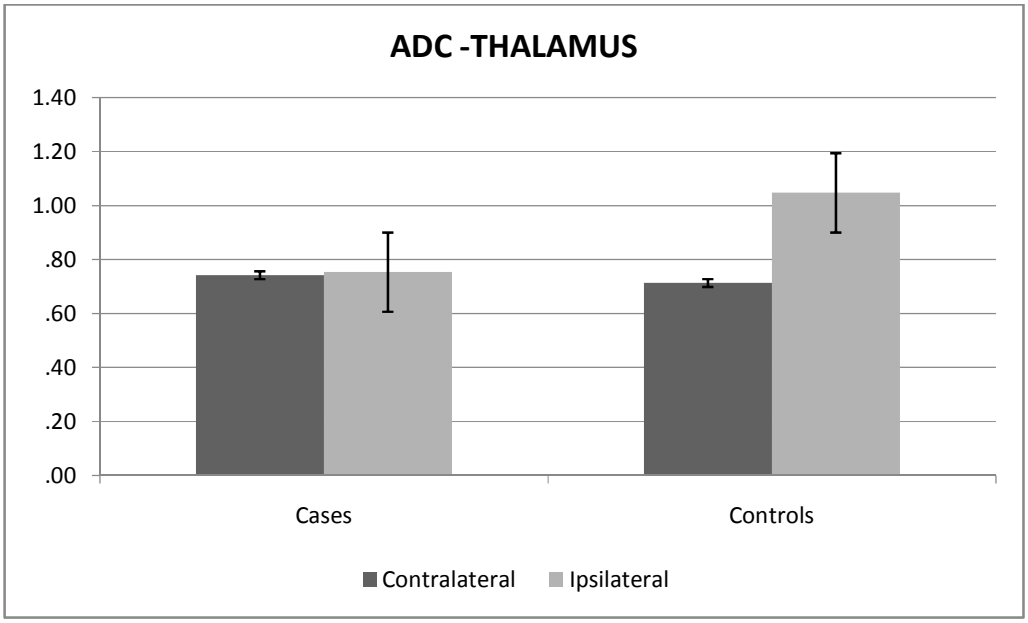


Figure 24. Error bar comparing FA of bilateral thalamus of cases and controls.

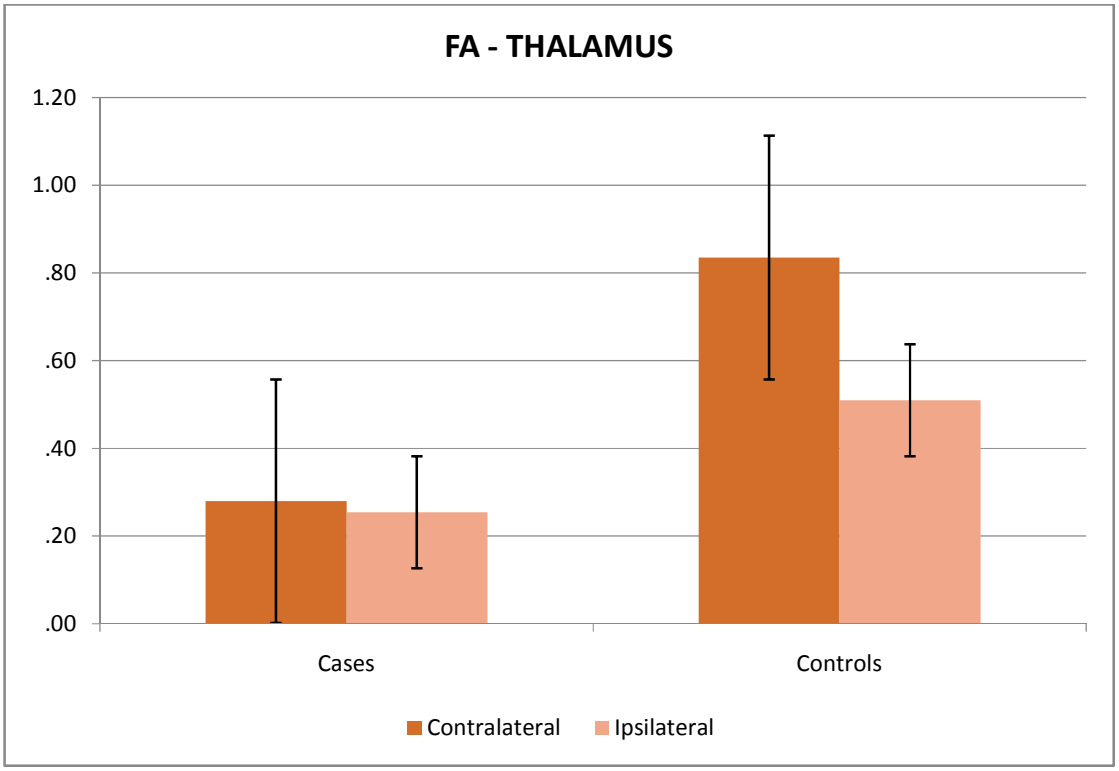


Table 9. FA & ADC OF INFERIOR FRONTO-OCCIPITAL FASCICULUS (IFO)

Site	Cases(21)	Cases(21)	Controls(10)	Controls(10)	P value
	Mean	SD	Mean	SD	
FA of ipsilateral infeior fronto-occipital	.51	.15	.67	.07	.001*
FA of contralateral infeior fronto-occipital	.54	.07	.62	.07	.000*
ADC of ipsilateral infeior fronto-occipital	.83	.17	.62	.07	.041*
ADC of contralateral infeior fronto-occipital	.81	.11	.64	.07	.039*

*statistically significant

Both FA and ADC values of bilateral frontal limbs of superior longitudinal fasciculi showed statistically significant values.

Figure 25. Error bar comparing ADC of bilateral inferior fronto-occipital of cases and controls

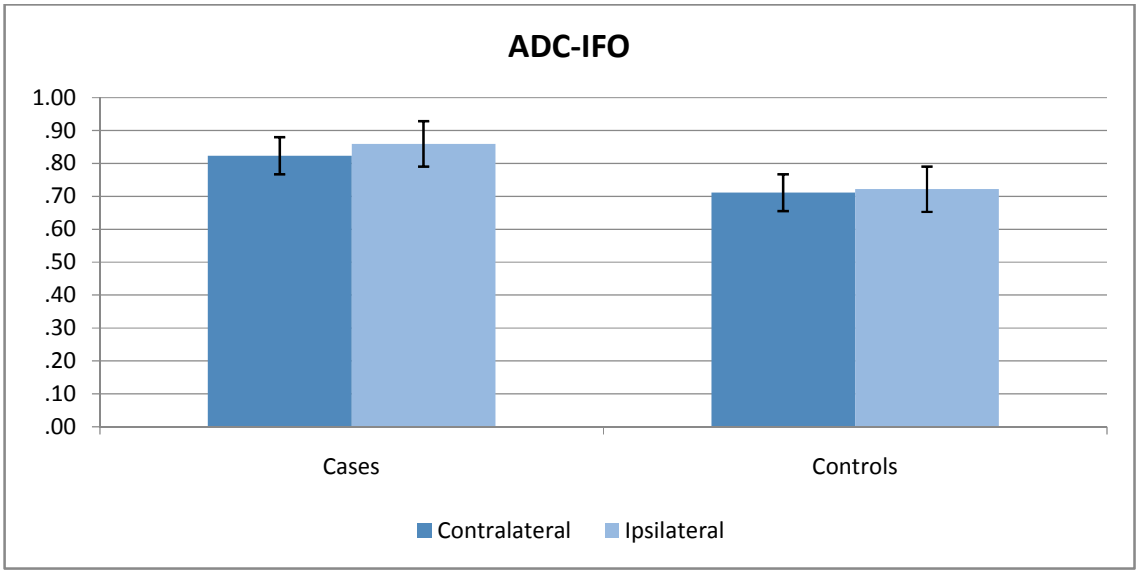


Figure 26. Error bar comparing FA of bilateral inferior fronto-occipital of cases and controls

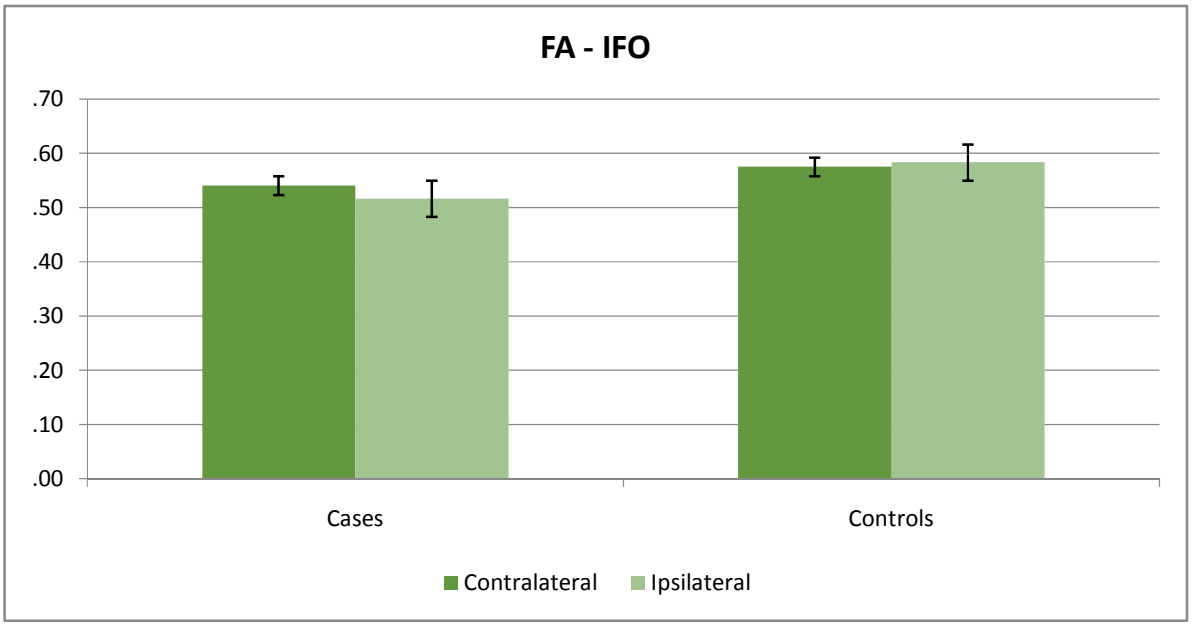


Table 10. FA & ADC INFERIOR TEMPORO-OCCIPITAL FASCICULUS

Site	Cases(21)	Cases(21)	Controls(10)	Controls(10)	P value
	Mean	SD	Mean	SD	
FA of ipsilateral inferior temporo-occipital fasciculus .	.45	.13	.50	.11	.000*
FA of contralateral inferior temporo-occipital fasciculus .	.49	.09	.53	.11	.002*
ADC of ipsilateral inferior temporo-occipital fasciculus .	.85	.09	.70	.12	.000*
ADC of contralateral inferior temporo-occipital fasciculus . fasciculus	.80	.12	.70	.12	.000*

*statistically significant

Compared to controls, patients' statical significant changes in Diffusion Tensor Imaging(DTI) matrices in inferior temporo-occipital fasciculus .

Figure 27. Error bar comparing ADC of bilateral inferior temporo-occipital fasciculus of cases and controls

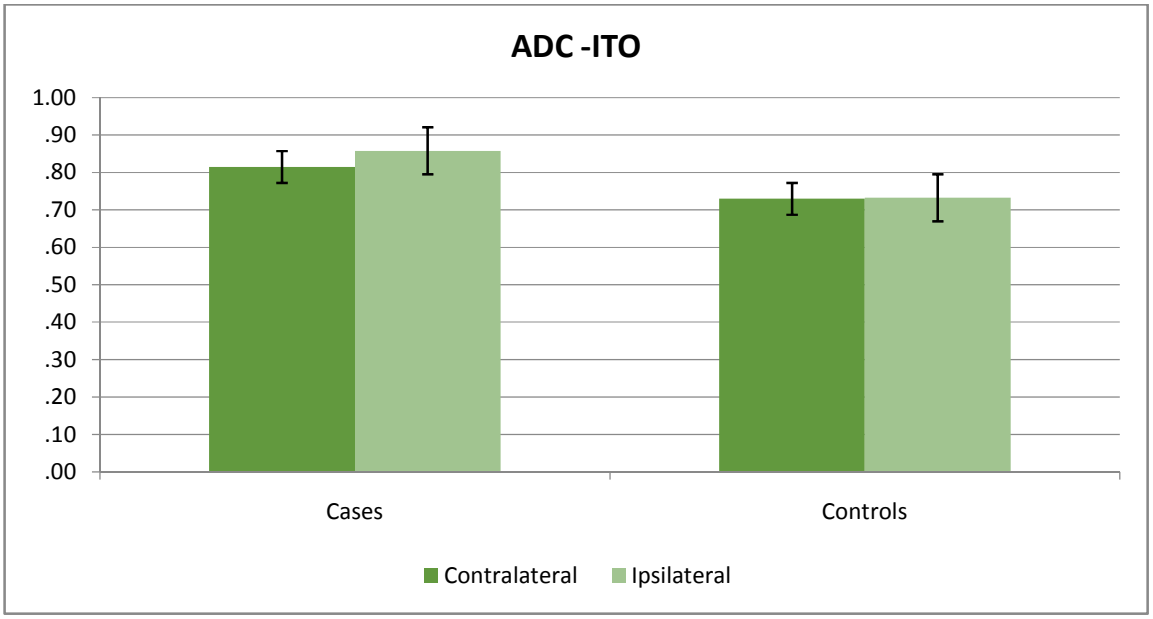


Figure 28. Error bar comparing FA of bilateral inferior temporo-occipital fasciculus of cases and controls

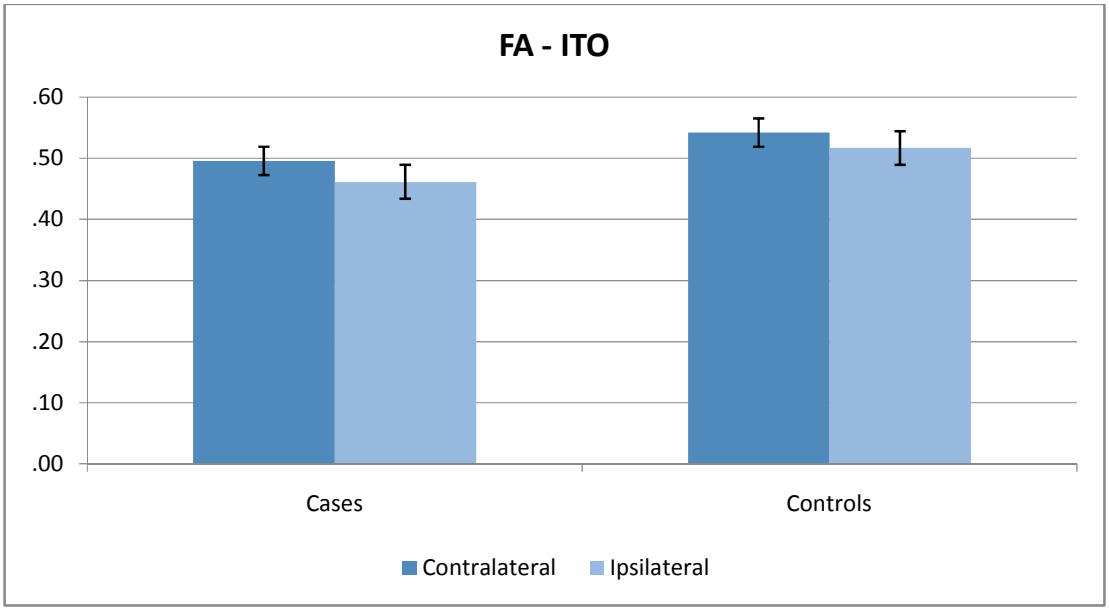


Table 11. FA & ADC OF UNCINATE FASCICULUS

Site	Cases(21)	Cases(21)	Controls(10)	Controls(10)	P value
	Mean	SD	Mean	SD	
FA of ipsilateral uncinate fasciculus	.32	.19	.49	.13	.003*
FA of contralateral uncinate fasciculus	.36	.14	.48	.13	.005*
ADC of ipsilateral uncinate fasciculus	.89	.39	.69	.79	.000*
ADC of contralateral uncinate fasciculus	.83	.15	.69	.79	.002*

*statistically significant

FA & ADC of ipsilateral uncinate fasciculus had statistically significant reduced and increased values respectively, in cases compared to controls.

Figure 29. Error bar comparing ADC of bilateral uncinate fasciculus of cases and controls

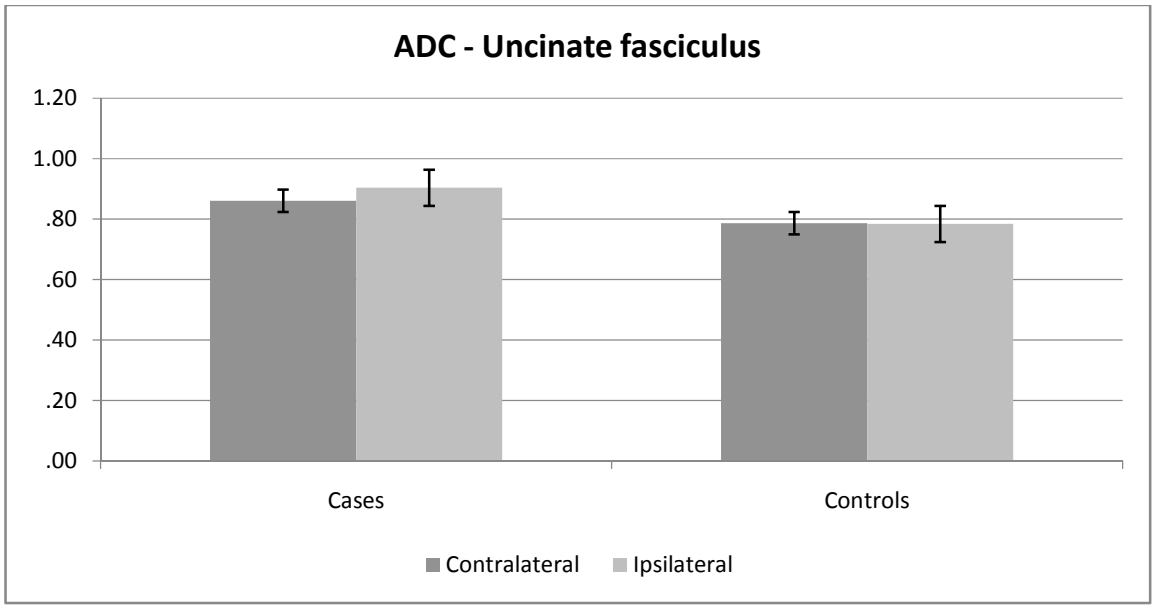


Figure 30. Error bar comparing FA of bilateral uncinate fasciculus of cases and controls

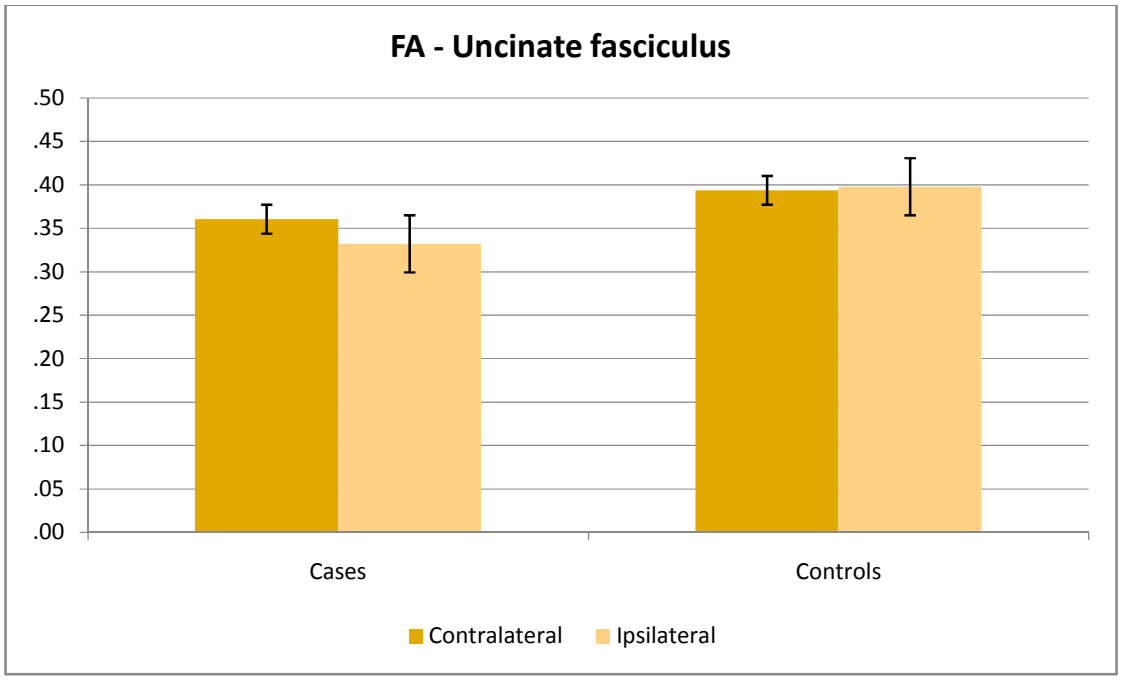


Table 12. FA & ADC OF MIDDLE CEREBELLAR PEDUNCLE

Site	Cases(31)	Cases(31)	Controls(30)	Controls(30)	P value
	Mean	SD	Mean	SD	
FA of ipsilateral middle cerebellar peduncle	.71	.11	.69	.09	.078
FA of contralateral middle cerebellar peduncle	.73	.11	.72	.09	.065
ADC of ipsilateral middle cerebellar peduncle	.71	.15	.68	.09	.02
ADC of contralateral middle cerebellar peduncle	.70	.14	.69	.09	.314

*statistically significant

FA of bilateral middle cerebellar peduncles showed there is no statistically significant reduced values compared to controls, ADC values though higher, did not reach statistical significance.

Figure 31.Error bar comparing ADC of bilateral middle cerebellar peduncle of cases and controls

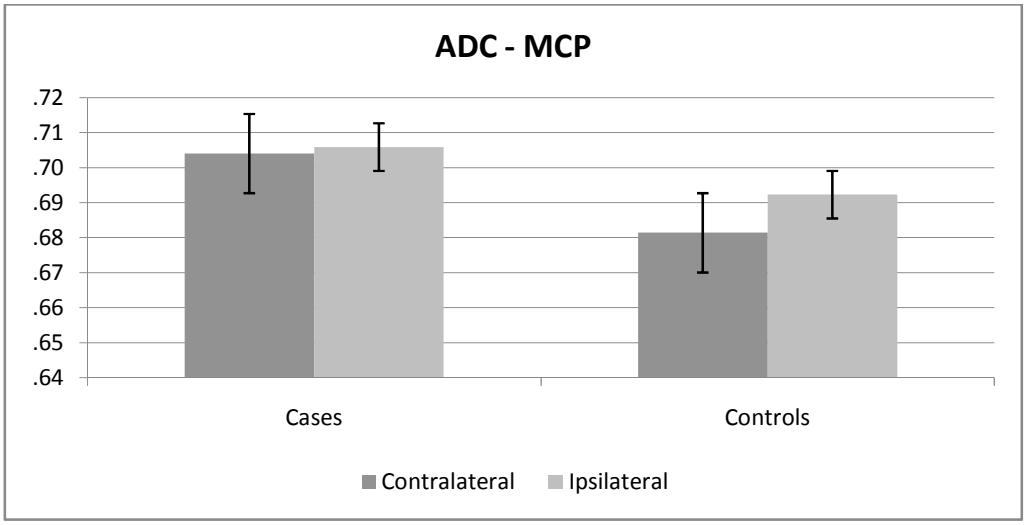


Figure 32.Error bar comparing FA of bilateral middle cerebellar peduncle of cases and controls

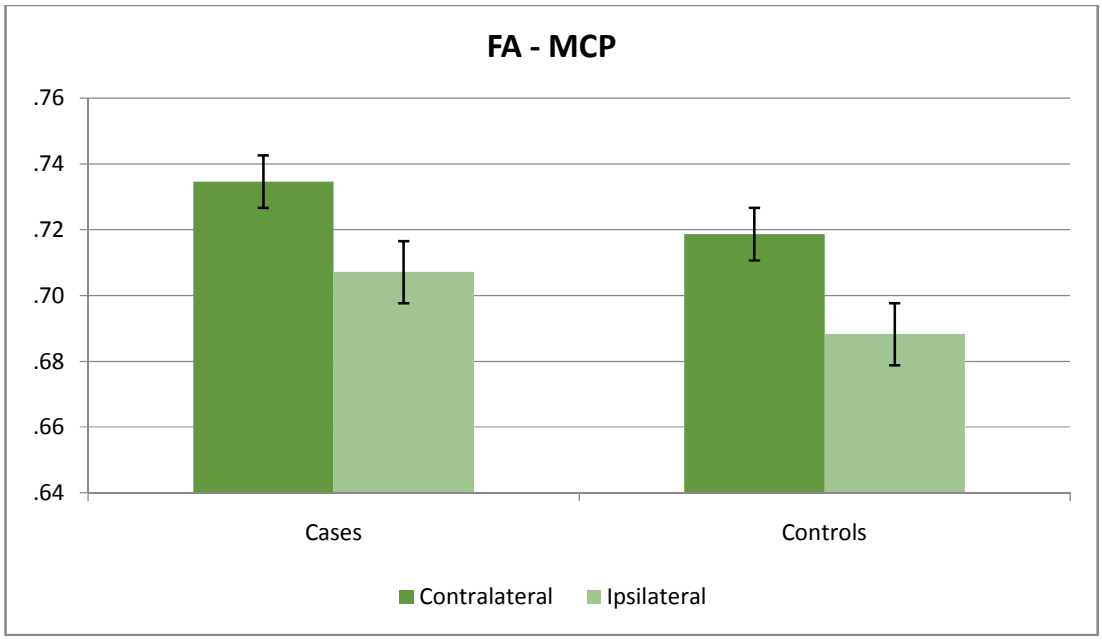


Table 13. FA & ADC OF ANTERIOR CINGULUM

Site	Cases(21)	Cases(21)	Controls(10)	Controls(10)	P value
	Mean	SD	Mean	SD	
FA of ipsilateral anterior cingulum	.33	.09	.44	.06	.000*
FA of contralateral anterior cingulum	.39	.11	.44	.06	.003*
ADC of ipsilateral anterior cingulum	.77	.10	.73	.14	.000*
ADC of contralateral anterior cingulum	.76	.14	.73	.14	.004*

*statistically significant

ADC&FA of bilateral anterior cingulum showed statistically significant reduced values compared to controls.

Figure 33. Error bar comparing ADC of bilateral anterior cingulum of cases and controls

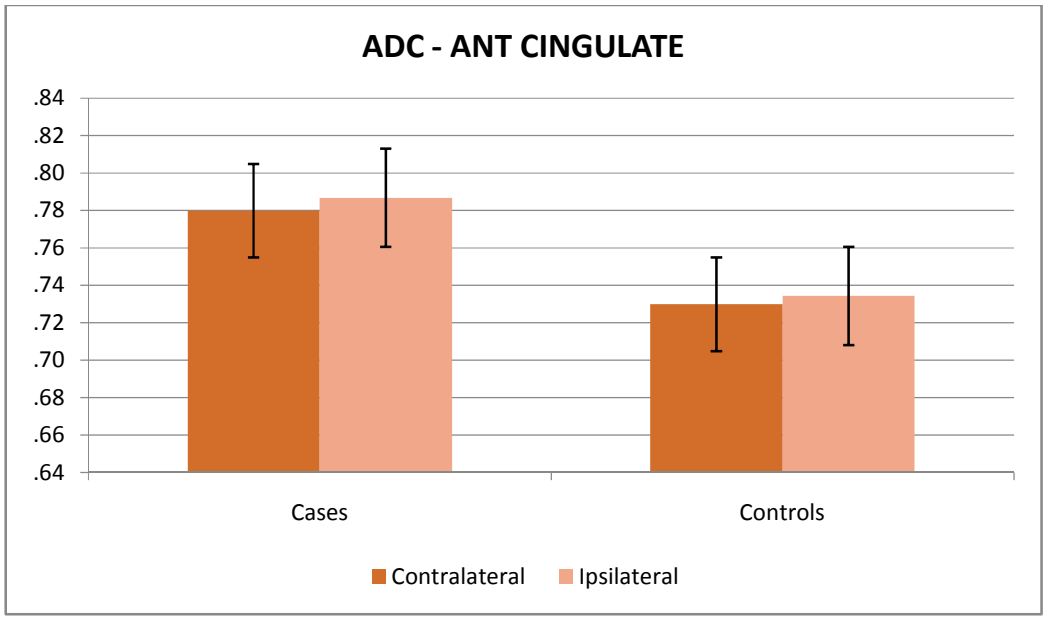


Figure 34. Error bar comparing FA of bilateral anterior cingulum of cases and controls

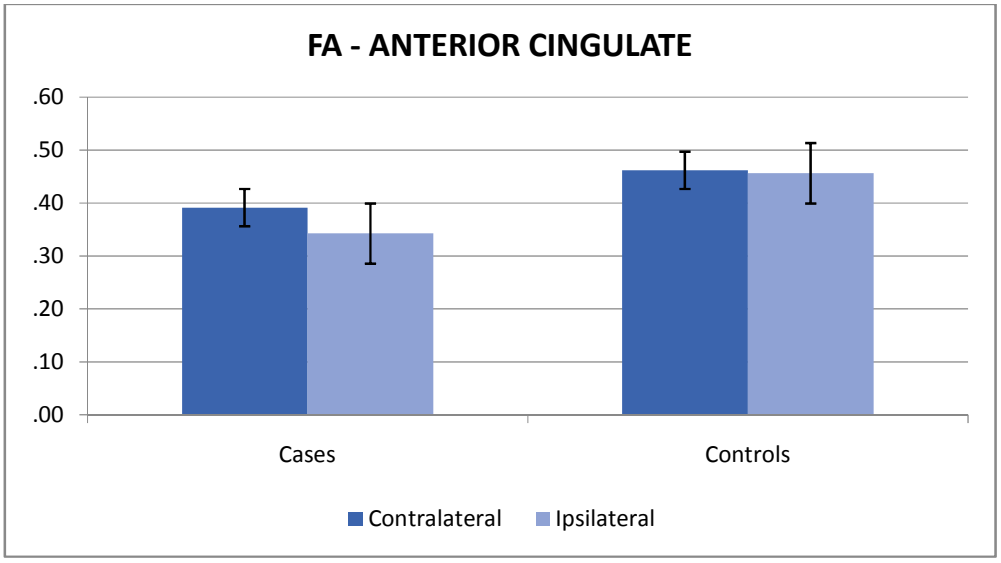


Table 14. FA & ADC OF POSTERIOR CINGULUM

Site	Cases(21)	Cases(21)	Controls(10)	Controls(10)	P value
	Mean	SD	Mean	SD	
FA of ipsilateral anterior cingulum	.39	.09	.48	.06	.002*
FA of contralateral anterior cingulum	.42	.11	.47	.06	.003*
ADC of ipsilateral anterior cingulum	.80	.10	.61	.14	.001*
ADC of contralateral anterior cingulum	.68	.14	.61	.14	.004*

*statistically significant

ADC & FA of bilateral posterior cingulum showed statistically significant reduced values compared to controls .

Figure 35. Error bar comparing ADC of bilateral posterior cingulum of cases and controls

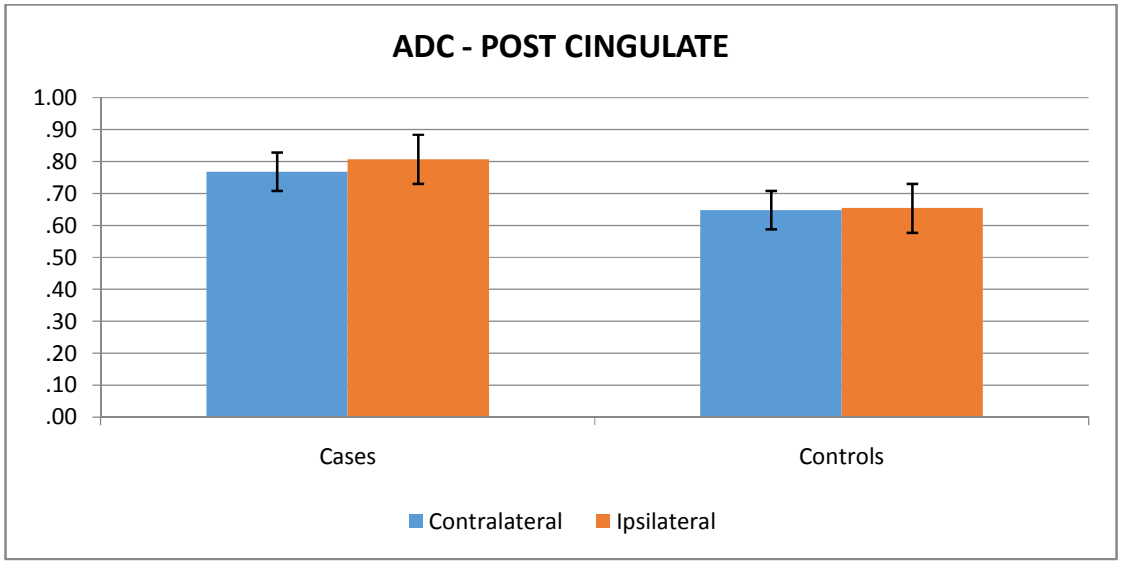


Figure 36. Error bar comparing FA of bilateral posterior cingulum of cases and controls

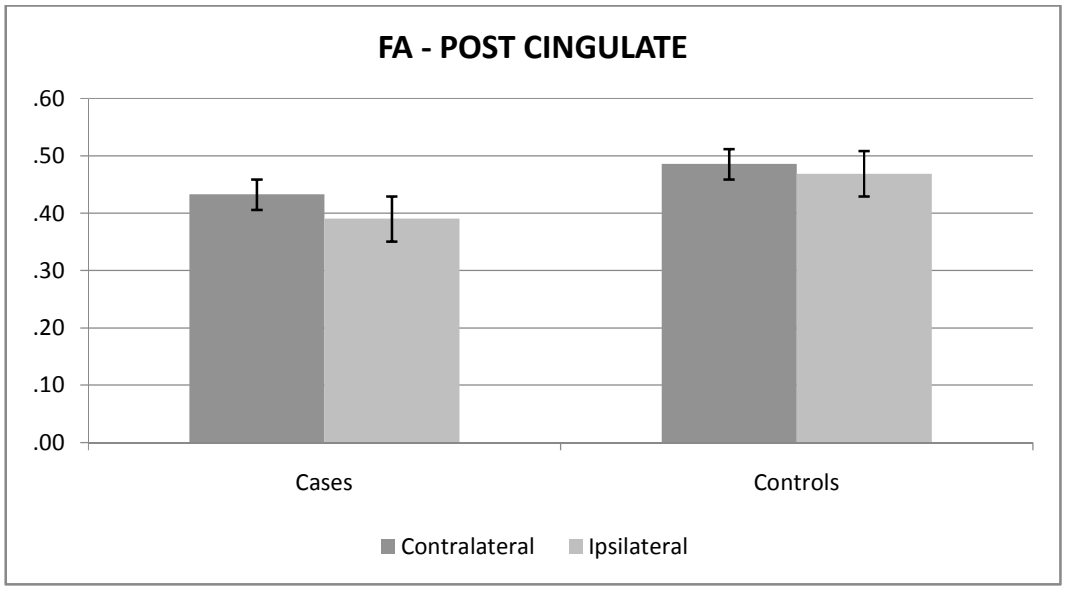


Table 15. FA & ADC OF PARAHIPPOCAMPAL GYRUS

Site	Cases	Cases	Controls	Controls	P value
	Mean	SD	Mean	SD	
FA of ipsilateral parahippocampal gyrus	.39	.12	.41	.14	.001*
FA of contralateral parahippocampal gyrus	.41	.18	.41	.14	.187
ADC of ipsilateral parahippocampal gyrus	.85	.11	.74	.13	.004*
ADC of contralateral parahippocampal gyrus	.81	.18	.74	.13	.003*

*statistically significant

ADC &FA values shows significant changes except for Fractional Anisotropy (FA) of contralateral parahippocampal gyrus, although it is decreased but not significantly.

Figure 37. Error bar comparing ADC of bilateral parahippocampus gyrus of cases and controls

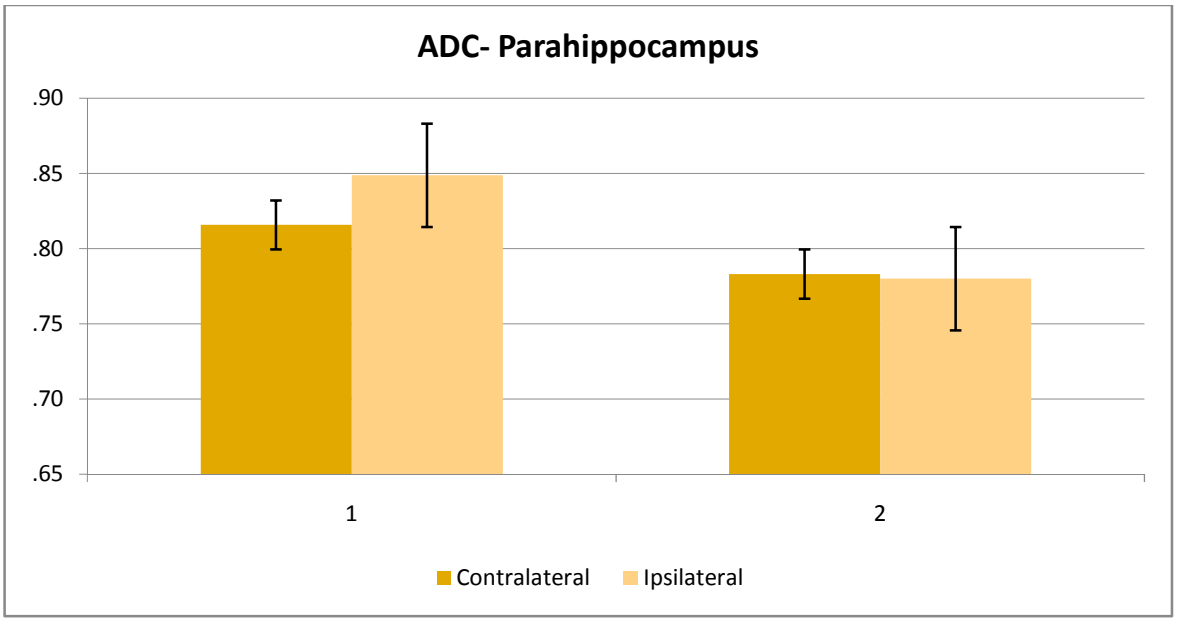
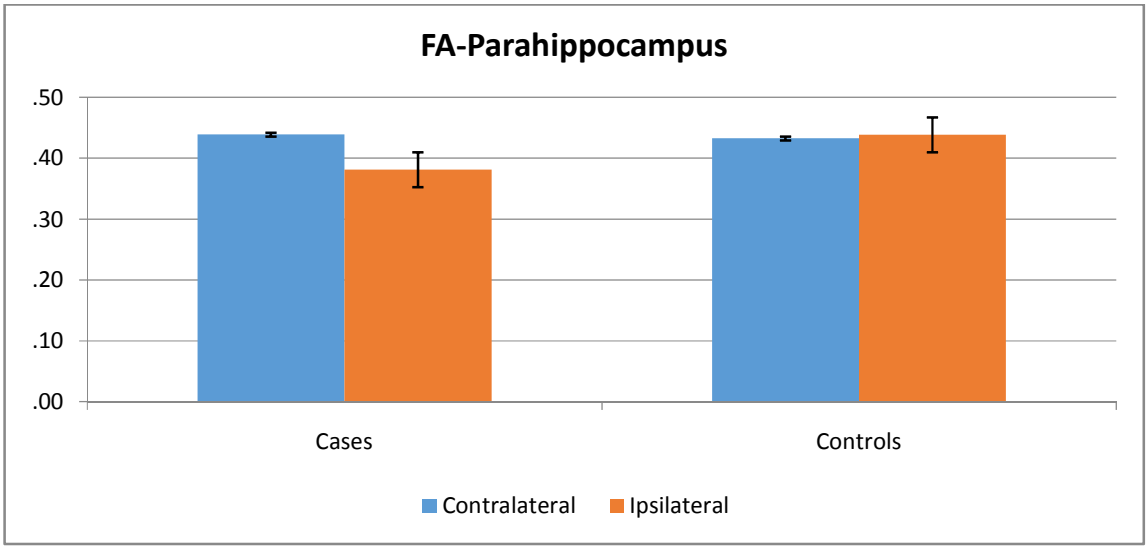


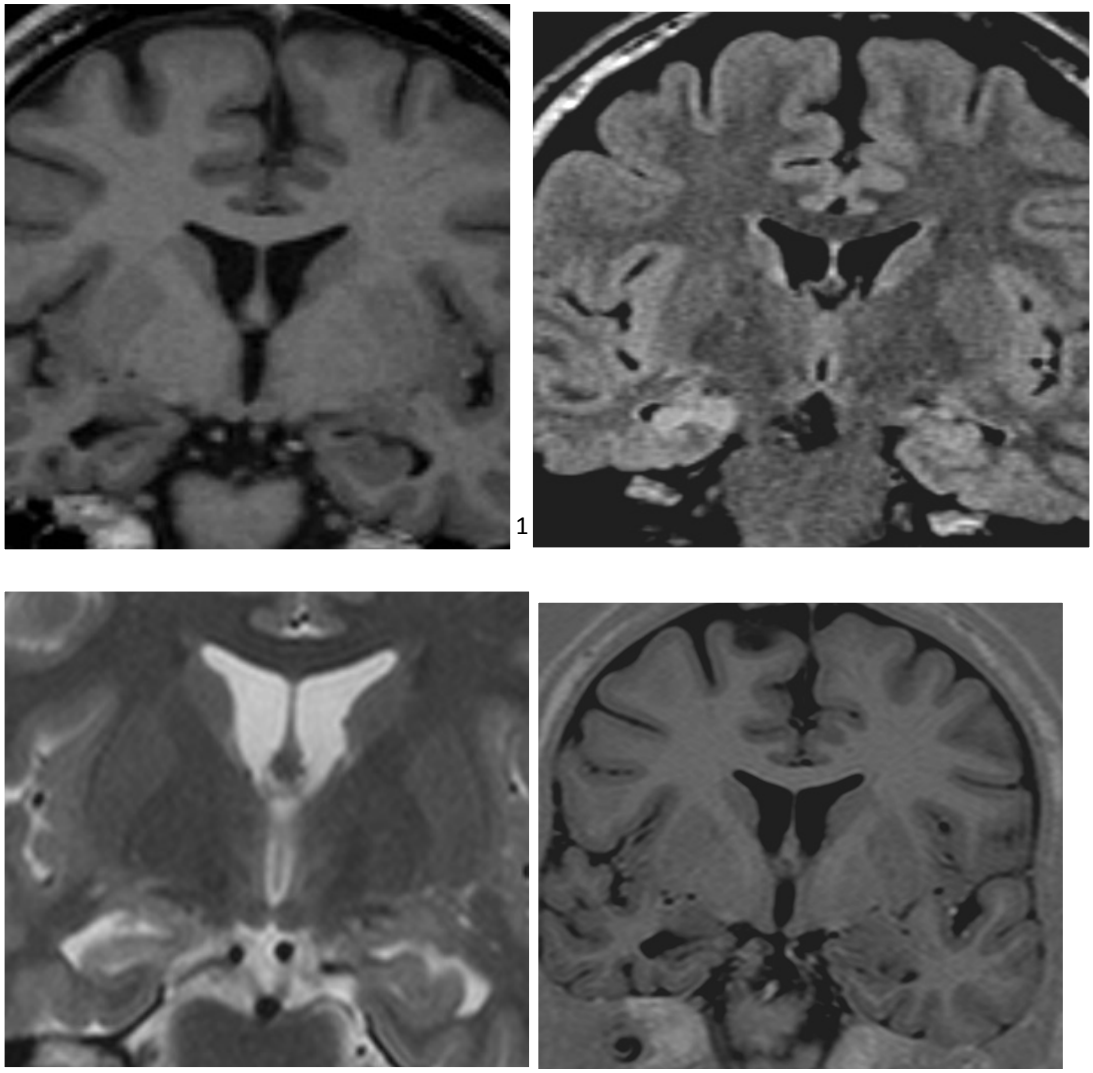
Figure 38. Error bar comparing FA of bilateral parahippocampus gyrus of cases and controls



Summary of results:

There is increased in ADC and reduced Fractional Anisotropy (FA) measurement noted in cases compared to controls and the Diffusion Tensor Imaging(DTI) values were more altered in ipsilateral structures . Most of the structures are showing statically significant changes except for the few like Contralateral Middle cerebral peduncle, Fractional Anisotropy (FA) of contralateral parahippocampal gyrus, ADC of contralateral head of caudate nucleus and ADC of contralateral fornix.

Cases



Figures 40 showing cases with right mesial temporal lobe sclerosis on MRI morphometry.

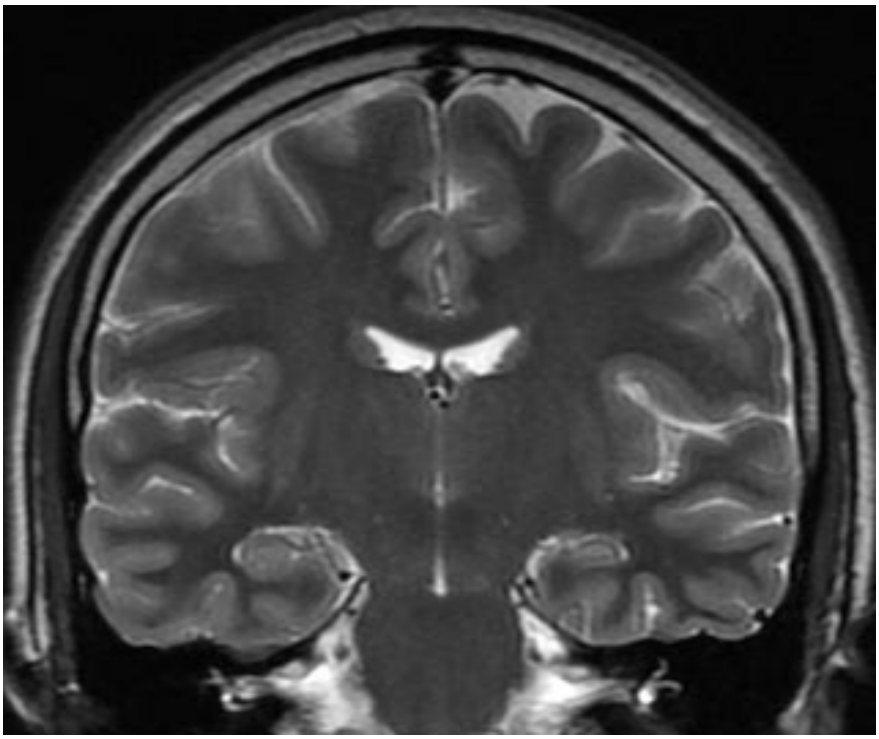


Figure 46 showing increased T2 intensity with small left hippocampus in patient with left temporal lobe epilepsy.

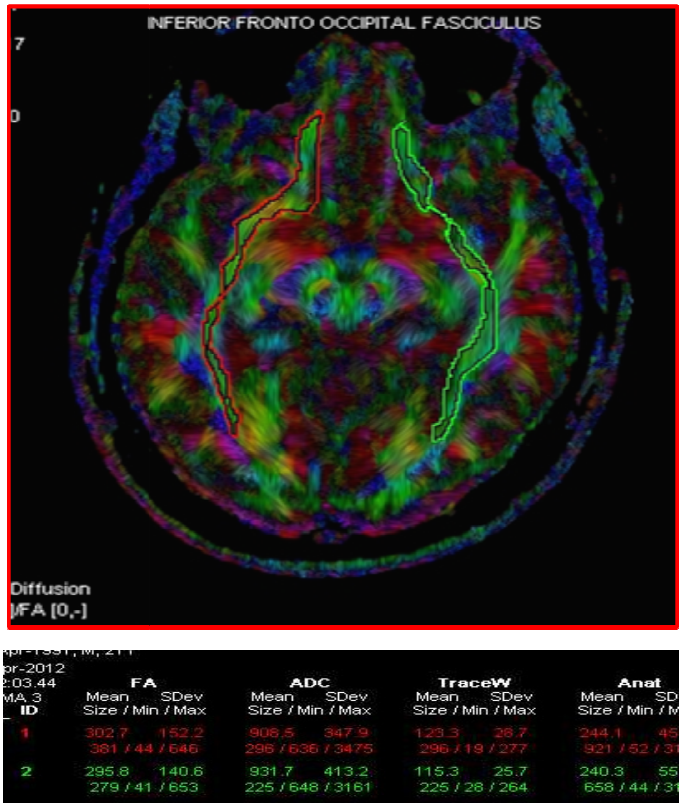


Fig. 41 showing region of interest in inferior fronto-occipital longitudinal fasciculus along with Diffusion Tensor Imaging(DTI) measurements

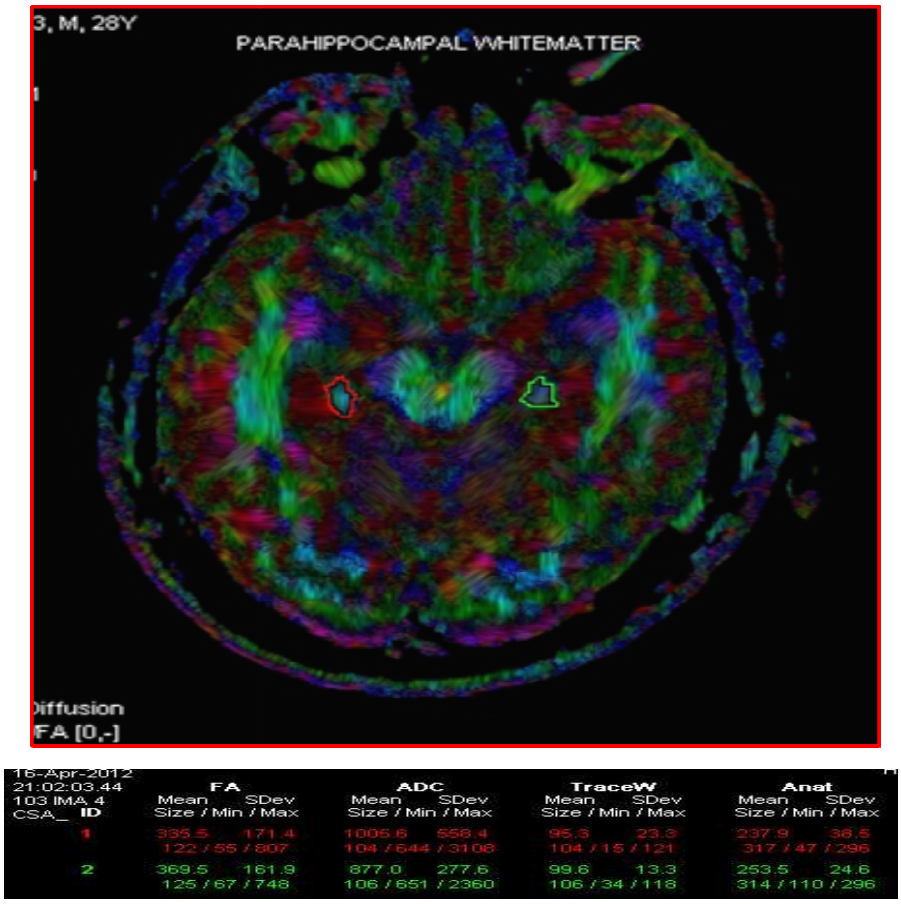


Fig. 41 showing region of interest in bilateral parahippocampus along with Diffusion Tensor Imaging(DTI) measurements

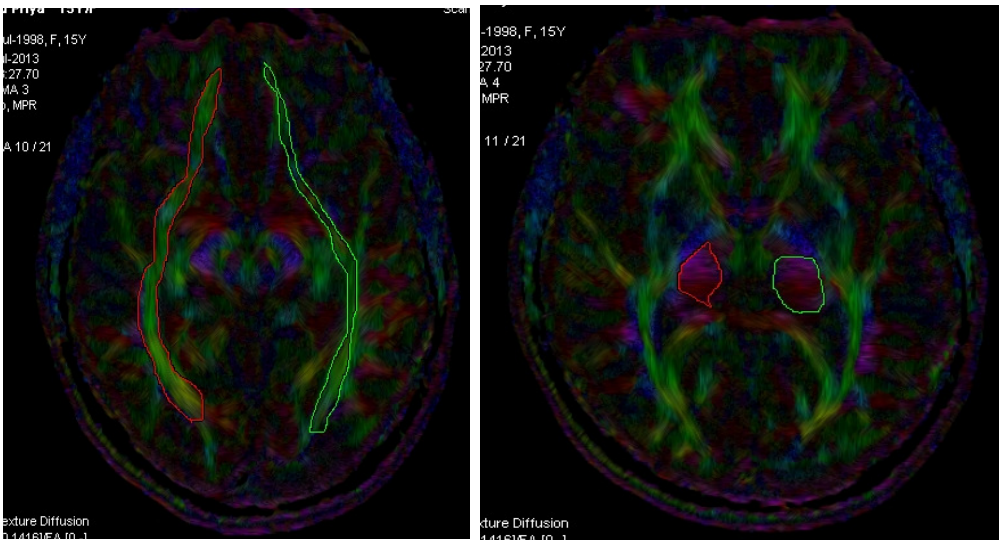


Fig 42. Showing color coded maps with Region of Interests (ROI) selected in superior fronto –occipital longitudinal fasciculus and thalamus.

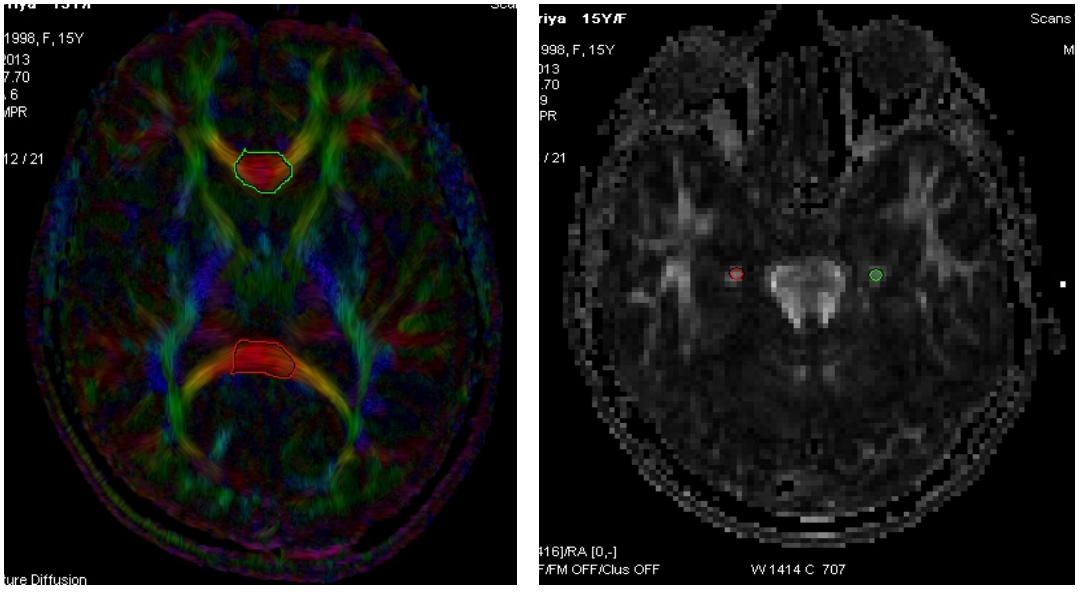
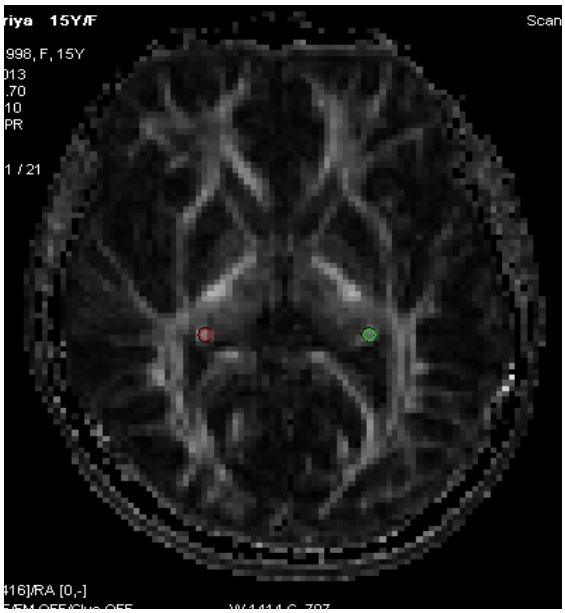
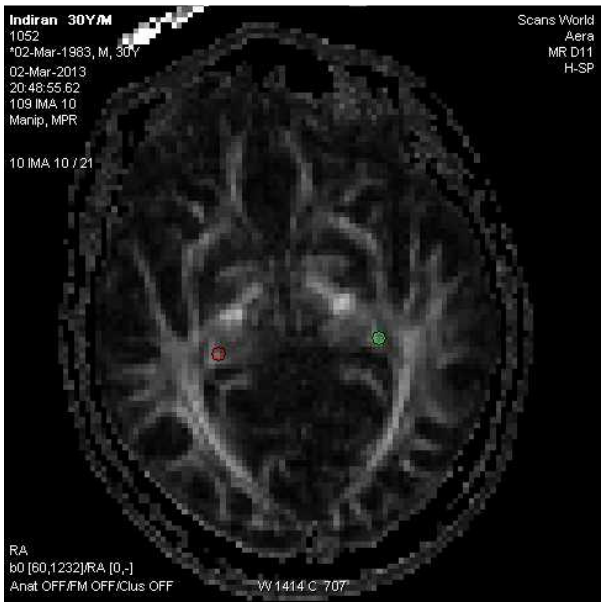
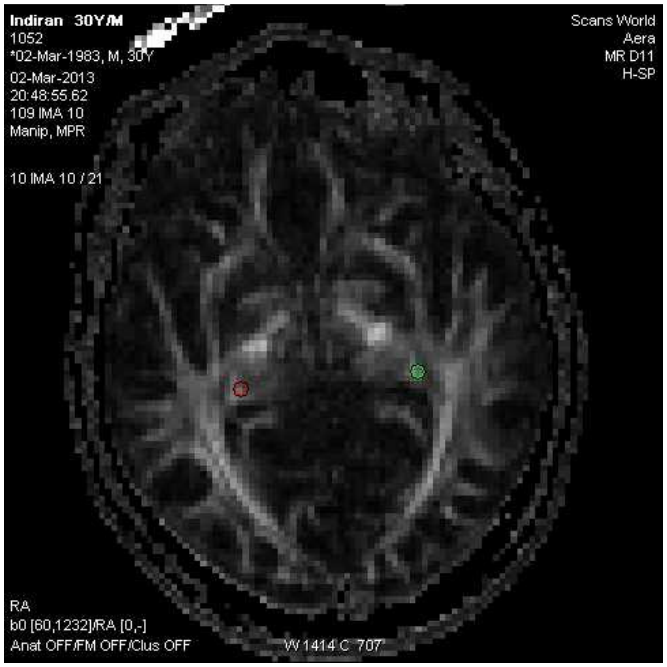


Fig 43 showing color coded Diffusion Tensor Imaging(DTI) map with Fractional Anisotropy (FA) maps with Region of Interests (ROI) in corpus (callosum genu and splenium) and parahippocampal white matter.







Figures 45 showing Fractional Anisotropy (FA) maps with Region of Interests (ROI) fimbrae and fornix.

DISCUSSION:

Temporal lobe epilepsy is the most common form of focal epilepsy. The hippocampus is a major source of seizure activity and microstructural alterations occur before they show up on conventional imaging[2]. During the ictal phase of seizures, there is an increase in oxygen consumption in the seizure focus, which is more than the increased blood flow. It results in relative ischemia and cytotoxic edema which is shown to result in decreased ADC. As time progresses, epilepsy results in neuroglia, increased extracellular space and increased interictal ADC[9]. Anisotropic diffusion is also reduced in the white matter tracts through which the epileptiform discharges travel, reducing the FA[9].

Diffusion tensor imaging,with its armamentarium of many indices is sensitive to identify these abnormalities. We have used the FA and ADC values of the hippocampi and various other grey and white matter tracts to study the hippocampal and extra hippocampal alterations.

The case group consisted of 21 patients with unilateral temporal lobe epilepsy, 10 males and 11 females, all the patients were diagnosed for unilateral mesial temporal lobe epilepsy and had EEG localised to the ipsilateral temporal lobe. The disease duration varied from one month to 15 years.

Hippocampal diffusivity and anisotropy:

The hippocampal indices of 21 patients with hippocampal sclerosis were compared with the 10 age matched controls. Patients' both ipsilateral and contralateral hippocampi had statistically significant reduced FA and increased ADC values. The results of our ipsilateral hippocampus is in line with the results of Thivard et al[17] and Assaf et al[2] in 2003 who also found increased mean diffusivity(ADC) in the ipsilateral hippocampus.

Assaf et al [2] with 12 patients of unilateral temporal lobe epilepsy found diffusivity measurements more sensitive than anisotropy. They observed that the selection of region of interest (ROI) in the anterior body of hippocampus yielded accurate and consistent measurement. ROI was placed in the anterior body of hippocampus in our study as per their recommendations.

Bilateral hippocampi are connected with each other through the hippocampal commissure and the anterior commissure through the fornices[27]. Many studies have demonstrated widespread propagation of seizure activity through the neuronal networks[9,10,11,12,13]. We have observed increased ADC and reduced FA in the contralateral hippocampus, the electrical activity possibly utilising the commissures.Previous studies with contralateral hippocampus have yielded varying results as observed by Thivard et al[17]. The results were either normal or reduced mean diffusivity. All our patients had visually recognisable

mesial temporal sclerosis, compared to Assaf et al[2] where one third had normal conventional MR findings. This reflects higher degree of structural damage in our cases and explain the bilaterally significant hippocampal values.

Though the contralateral hippocampus shows statistically significant diffusion tensor imaging indices, no such changes could be demonstrated in the contralateral fornices in our study. We had technical difficulties in placing the voxel exclusively within the fornix without contamination from the CSF, which might be responsible for the insignificant values. But our results concur with those of Thivard et al[17] who did not find significant values in bilateral fornices.

Concha L et al [24] in 2010 with 11 medically intractable TLE patients with and without hippocampal sclerosis, found positive correlation between diffusivity of fimbria - fornix and histology. DTI was acquired following an inversion pulse (TI 2200 ms at 1.5T) to suppress the cerebrospinal fluid signal, which likely yielded them accurate results.

Comparison of extratemporal grey matter of patients and controls:

We analysed the FA and ADC values of bilateral thalami, head of caudate nucleus and lentiform nucleus of all our 21 patients and compared them with 10 controls. We observed increased ADC and decreased FA in bilateral lentiform nuclei and the ipsilateral caudate nucleus. ADC of contralateral head of caudate nucleus was higher but did not achieve statistical significance. FA of bilateral head of caudate nucleus was decreased with

statistically significance. Our ADC results are in line with Yin et al[9] who got significantly altered values in the caudate nucleus and that of Chen Q et al[13] who concluded that mean diffusivity is more sensitive than fractional anisotropy.

Statistical significance was seen in the thalamus. Thivard et al[17] with statistic parametric mapping explored the whole brain diffusion tensor imaging indices and found no statistically significant changes in the thalami. Our thalamic results doesn't concur with their results. Yin et al[9] had insignificant ADC values, which doesn't concur with our results, the reason possibly may be advance stages of our cases as all cases were having morphological abnormalities..

Comparison of extra temporal white matter of patients and controls:

Though the seizure onset is located within the temporal lobe, through the widespread interaction between cortical and subcortical structures, the epileptic circuitry is widened. Though structural abnormalities were limited to ipsilateral hippocampus and the temporal lobe, widespread diffusion abnormalities were seen in bilateral white matter in our study.

The major extra temporal diffusion abnormalities in our study consists of reduced FA in bilateral anterior limb of internal capsule, body , genu and splenium of corpus callosum, bilateral inferior temporo-occipital fasciculus, bilateral superior fronto –occipital longitudinal fasciculus, bilateral uncinate fasciculus, ipsilateral middle cerebellar peduncle and bilateral cingulum.

Increased ADC values are seen in bilateral anterior limb of internal capsule, body , genu and splenium of corpus callosum, bilateral inferior temporo-occipital fasciculus, bilateral superior fronto –occipital longitudinal fasciculus, bilateral uncinate fasciculus, ipsilateral middle cerebellar peduncle and bilateral cingulum.

Our present data are in agreement with Knake et al[28] who observed lower FA values in body/ trunk of corpus callosum, ipsilateral frontal and bilateral temporal lobes. They used both ROI method and whole brain analysis. The results of both methods were complementary to each other. Whole brain analysis picks up confluent changes but is insensitive to small focal changes. ROI method requires precise placement in the predetermined area. We used manually placed ROIs on preselected regions.

Our results of temporal lobe white matter concur with those of Rileyetal[16] and Thivard et al [17] who also observed increased diffusivity and reduced anisotropy along the temporal white matter. Thivard et al [17] were the first to describe the extra hippocampal temporal white matter diffusion changes. They found no modification in the FA for the hippocampal/parahippocampal region. In our study, there was significant change in the ADC and FA values of hippocampus, though the parahippocampal region did not demonstrate significant alterations.

We have obtained significant FA and ADC values in bilateral frontal lobe white matter. This shows early and preferential spread to frontal lobes through uncinate fasciculus in nearly all cases.The study by Wang et al[18] with 27 temporal lobe epilepsy patients showed impaired category fluency and other executive functions compared to controls. They concluded that propagation of seizures to frontal lobe, not detected by standard MRI as the reason behind impaired category fluency. Though executive functions were not tested in our patients, frontal white matter involvement implies impaired executive function.

We had statistically significant FA values in bilateral cingulum, a major hippocampal pathway. This is in line with the results of Thivard et al[17]who observed statistically significant differences in the cingulum.

Corpus callosum is the major commissural fibre connecting the two hemispheres. Our study revealed statistically significant changes in both ADC and FA values in the body, splenium and genu of corpus callosum. Knake et al[28] observed reduced FA in the genu and body of corpus callosum, Thivard et al[17] found reduced FA in corpus callosum, Meng et al[12] got reduced FA and increased ADC in the splenium, Yin et al[9] had lower FA in genu, body and splenium with higher diffusivity in body of corpus callosum. Kim et al[11] with ten patients of temporal lobe epilepsy found reduced FA values in the splenium, so our study concur with above studies.

Internal capsule is a major projection fibre. We observed statistically significant reduced FA and increased ADC values in bilateral anterior limb as well as bilateral posterior limbs. Of the previous studies, Meng et al[12] observed reduced FA and increased diffusivity values in anterior limb, posterior limb and the genu, Yin et al[9] showed lower FA in the anterior and posterior limbs of internal capsule, Wang et al[18] found lower FA in left posterior limb, Meng et al[12] observed increased diffusivity and reduced FA in anterior and posterior limbs.

Regions in violet represent concurrence with our study.

Uncinate fasciculus is a major white matter tract connecting anterior temporal and frontal lobes. It is important in the formation and retrieval of memories and is a pathway for seizure spread to the frontal lobe[14]. In our study, bilateral uncinate fasciculus had reduced FA and increased ADC values. Diehl et al[14], in 2008 analysed the DTI parameters of 28 TLE patients and correlated them with auditory and visual, immediate and delayed memory. They found significant alterations in diffusion tensor imaging indices in bilateral uncinate fasciculi correlated with memory in patients with left TLE (both medial and lateral).The involvement of uncinate fasciculus in our cases, implies impaired memory, though we did not directly test for memory.

Patients with temporal lobe epilepsy have multiple cognitive impairments like memory, executive functions, language, intelligence and motor speed[16]. Riley et al in 2010[16] studied the integrity of white matter tracts using whole brain FA and its impact on the cognitive function in 12 TLE patients. They found white matter abnormalities in fornix, uncinate and

arcuate fasciculus, inferior longitudinal fasciculus, motor projection fibres and the cerebellum. These abnormalities correlated with the cognitive performance. In our study, we had significant reduced FA in bilateral middle cerebellar peduncle, temporal and occipital regions of bilateral inferior longitudinal fasciculus, ipsilateral uncinate fasciculus concurring with their study. We did not test the cognitive profiles of our patients, it is an area of future research in our region.

Gross et al[20], in their meta-analysis of 10 studies observed that though the cause and implications of white matter changes are unclear, they represent downstream axonal degeneration secondary to spreading seizure activity. They also observed that the changes are variable between studies in grey and white matter tract involvement and represent variations in patient selection, methodology, duration and propagation of seizure activity. The duration of seizures in our patients ranged from one month to 15 yrs.

LIMITATIONS OF OUR STUDY:

1. The study was done on patients being ictus free for at least a week, as ictus is shown to affect ADC values. However, subclinical seizures, not identified, could have occurred with impact on our values.

2. In this study, diffusion tensor imaging was done in 21 non collinear directions. Increasing the number of directions might increase the yield of the study.

3. There was technical difficulties in placing the voxel on fornix without contamination from CSF as the size of single voxel was larger than the fornix.

4. The results are population based, so the application as a clinical tool in the management of patients remains unexplored.

5. Duration and compliance with treatment and seizure frequency may affect the FA and ADC values. These were not included as variables in this study.

6. Number of controls could be increased .

RECOMMENDATIONS:

1. Diffusion tensor imaging can be incorporated in routine epilepsy protocol as altered hippocampal values adds to the diagnosis in equivocal cases. Moreover, there is widespread bilateral alterations in the FA and ADC values, though conventional imaging shows abnormality restricted to ipsilateral temporal lobe.
2. The number of directions may be increased, instead of 21, as it might yield better results.
3. DTI can be done with fluid suppression to avoid CSF contamination for obtaining values from the fornices.
4. Cognition tests can be done from the onset of epilepsy and correlated with DTI, it might help in prognostication.
5. Longitudinal studies can be undertaken in patients with recent onset epilepsy,as it can better define the progression of white matter changes.

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ANNEXURES

Abbreviations

DTI : diffusion tensor imaging.

FA : fractional anisotropy.

CC : corpus callosum

IFO : Inferior fronto- occipital fasciculus

ITO : inferior temporo- occipital fasciculus

PROFORMA

Sr No. NAME/ AGE/SEX - DATE- / /

CLINICAL HISTORY-
CLINICAL DIAGNOSIS-

EEG-

MRI DIAGNOSIS-

DTI MEASURMENTS

STRUCTURE	RIGHT FA	RIGHT ADC	LEFT FA	LEFT ADC	ABNORMAL SIDE	COMMENT
1. Middle cerebellar peduncle (MCP)						
2. Uncinate fasciculus (U)						
3. Inferior fronto occipital fasciculus (FO)						
4. Inferior temporo occipital fasciculus (TO)						
5. Para hippocampal white matter (PH)						
6. Fimbria (FB) & Fornix (FX).						
7. Arcuate fasciculus						
8. Caudate Nucleus						
9. Lentiform nucleus						
10. Posterior internal capsule						
11. Corpus callosum (splenium)						
12. Corpus callosum (body)						
13. Corpus callosum (genu)						
14. thalamus						

REMARKS-

Role of Diffusion Tensor Imaging(DTI) Epilepsy

AT GOVERNMENT STANLEYMEDICAL COLLEGE HOSPITAL, CHENNAI.

INFORMED CONSENT

Place of study: Govt. Stanley medical college, Chennai

I ……. have been informed about the details of the study in my own language.

I have completely understood the details of the study.

I am aware of the possible risks and benefits, while taking part in the study.

I agree to collect samples of blood/saliva/urine/tissue if study needs.

I understand that I can withdraw from the study at any point of time and even then, I can receive the medical treatment as usual.

I understand that I will not get any money for taking part in the study.

I will not object if the results of this study are getting published in any medical journal, provided my personal identity is not revealed.

I know what I am supposed to do by taking part in this study and I assure that I would extend my full cooperation for this study.

Volunteer:	Witness:
Name and address	Name and address
Signature/thumb impression:	Signature/thumb impression
Date:	Date:

Investigator Signature and date

சுய ஒப்புதல் படிவம்

ஆய்வு செய்யப்படும் தலைப்பு :

D.T.I மூலம் மூளையில் ஏற்படும் வலிப்பு நோயை ஆய்வு செய்தல்

ஆராய்ச்சி நிலையம் :கதிர் வீச்சு இயல்துறை,

தமிழ்நாடு அரசு ஸ்டான்லி மருத்துவக்கல்லூரி & மருத்துவமனை,

சென்னை - 600 001.

பங்கு பெறுபவரின் பெயர் :

பங்குபெறுபவரின் எண்:

பங்கு பெறுவர் இதனை (✓) குறிக்கவும்.

மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. என்னுடைய சந்தேகங்களை கேட்கவும், அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டது.

நான் இவ்வாய்வில் தன்னிச்சையாகதான் பங்கேற்கிறேன். எந்த காரணத்தினாலோ எந்த கட்டத்திலும் எந்த சட்ட சிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகி கொள்ளலாம் என்றும் அறிந்து கொண்டேன்.

இந்த ஆய்வு சம்மந்தகமாகவோ, இதை சார்ந்த மேலும் ஆய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். நான் ஆய்வில் இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன்.

இந்த ஆய்வின் மூலம் கிடைக்கும் தகவல்களையும், பரிசோதனை முடிவுகளையும் மற்றும் சிகிச்சை தொடர்பான தகவல்களையும் மருத்துவர் மேற்கொள்ளும் ஆய்வில் பயன்படுத்திக்கொள்ளவும் அதை பிரசுரிக்கவும் என் முழு மனதுடன் சம்மதிக்கிறேன்.

இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக்கொள்கிறேன். எனக்கு கொடுக்கப்பட்ட அறிவுரைகளின்படி நடந்து கொள்வதுடன் இந்த

ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்றும் உறுதியளிக்கிறேன். என் உடல் நலம் பாதிக்கப்பட்டாலோ அல்லது எதிர்பாராத வழக்கத்திற்கு மாறான நோய்க்குறி தென்பட்டாலோ உடனே அதை மருத்துவ அணியிடம் தெரிவிப்பேன் என உறுதி அளிக்கிறேன்.

பங்கேற்பவரின் கையொப்பம் ..... **இடம்** ..... **தேதி**

கட்டைவிரல் ரேகை

பங்கேற்பவரின் பெயர் மற்றும் விலாசம் .....

ஆய்வாளரின் கையொப்பம் ..... **இடம்** ..... **தேதி**

ஆய்வாளரின் பெயர் .....

INSTITUTIONAL ETHICAL COMMITTEE,
STANLEY MEDICAL COLLEGE, CHENNAI-1

Title of the Work : Role of DTI in Epilepsy.

Principal Investigator : Dr. Prem Chand

Designation : PG in MD (Radio Diagnosis)

Department : Department of Radio Diagnosis
Government Stanley Medical College,
Chennai-01

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 02.07.2014 at the Council Hall, Stanley Medical College, Chennai-1 at 2PM

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate from the area of the work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4. You should abide to the rules and regulation of the institution(s).
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of the work.

MEMBER SECRETARY,
IEC, SMC, CHENNAI

MEMBER SECRETARY
ETHICAL COMMITTEE,
STANLEY MEDICAL COLLEGE
CHENNAI-600 001.

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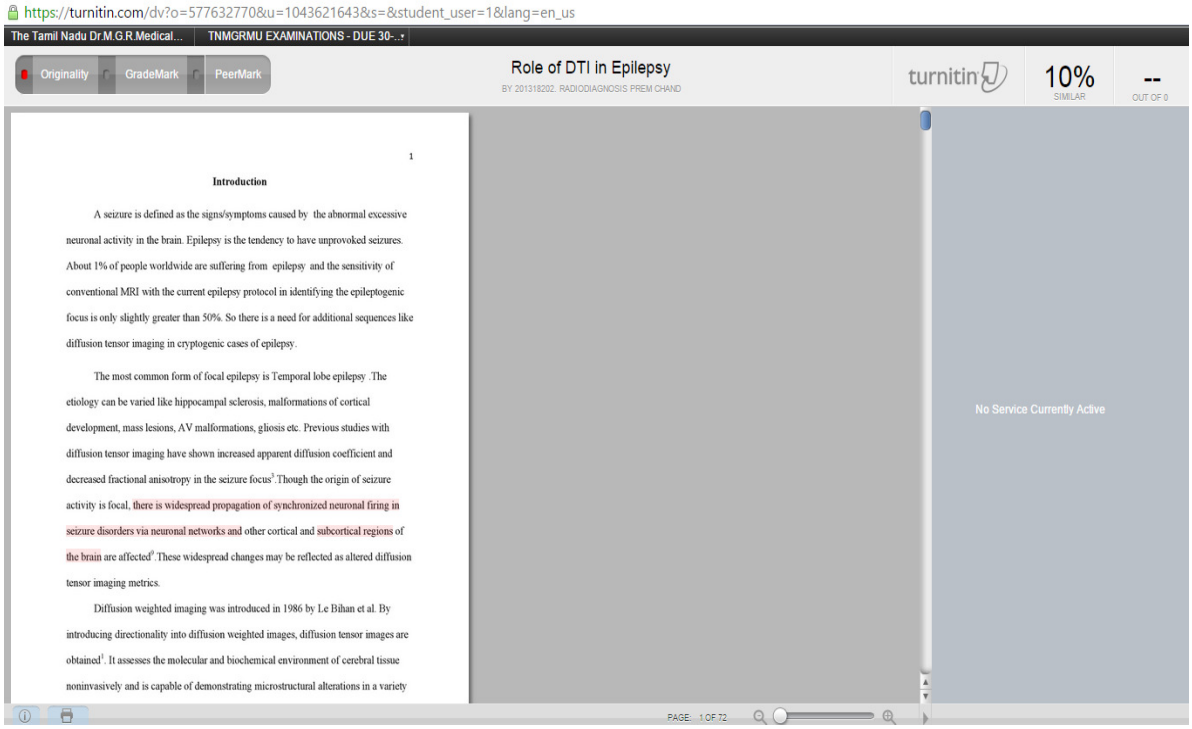

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« Page 1 »

Introduction

A seizure is defined as the signs/symptoms caused by the abnormal excessive neuronal activity in the brain. Epilepsy is the tendency to have unprovoked seizures. About 1% of people worldwide are suffering from epilepsy and the sensitivity of conventional MRI with the current epilepsy protocol in identifying the epileptogenic focus is only slightly greater than 50%. So there is a need for additional sequences like diffusion tensor imaging in cryptogenic cases of epilepsy.

The most common form of focal epilepsy is Temporal lobe epilepsy. The etiology can be varied like hippocampal sclerosis, malformations of cortical development, mass lesions, AV malformations, gliosis etc. Previous studies with diffusion tensor imaging have shown increased apparent diffusion coefficient and decreased fractional anisotropy in the seizure focus[1].Though the origin of seizure activity is focal, there is widespread propagation of synchronized neuronal firing in seizure disorders via neuronal networks and other cortical and subcortical regions of the brain are affected[2].These widespread changes may be reflected as altered diffusion tensor imaging metrics.

Diffusion weighted imaging was introduced in 1986 by Le Bihan et al. By introducing directionality into diffusion weighted images, diffusion tensor images are obtained[3]. It assesses the molecular and biochemical environment of cerebral tissue noninvasively and is capable of demonstrating microstructural alterations in a variety of disorders.

Colour coded fractional anisotropy maps and diffusion tensor imaging tractography are used in depicting the relationship of masses to adjacent white matter